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UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON MARINE NATURAL PRODUCTS

BY

GERARDO ULIBARRI ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1991

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FACULTY OF GRADUATE STUDIES AND RESEARCH

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To my parents because they believed in me

and

to human kind, that in this life my work

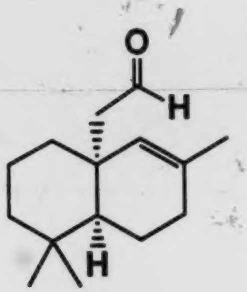
is helpful to its well-being.

Abstract

The first chapter of this thesis describes the first total synthesis of (±)-isoacanthodoral (**3**), a sesquiterpene aldehyde isolated from the dorid *Acanthodoris nanaimoensis*. The framework of compound **3** was built up starting from the Diels-Alder reaction of 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**12**) and isoprene. When the reaction was run in the presence of boron trifluoride etherate compounds **13** and **14** were obtained in a 3 : 7 ratio. Keto ester **14** was transformed into isoacanthodoral in 14 steps. Hydrosilylation of compound **14** followed by hydrolysis, reduction of the resulting ketone, xanthate formation and tri-*n*-butyltin hydride reduction gave ester **24**. Unsuccessful attempts to convert compound **24** into isoacanthodoral via the sequence of chain extension and then double bond isomerization are described. The successful approach involves the acid treatment of compound **24** to produce the key lactone **30**, which was reduced to diol **31**. Protection of the primary alcohol, dehydration and deprotection produced alcohols **26** and **35**. Compound **35** was converted into isoacanthodoral via the oxidation of the alcohol into an aldehyde, followed by a chain extension using a Wittig reaction and hydrolysis of the resulting enol ethers **37** and **38**.

The second chapter describes the studies directed towards the total synthesis of spirodysin (**46**), a marine natural product which

contains a spiro [5.5] and a *cis*-fused 5,6-bicyclic systems. Unsuccessful attempts to obtain the 5,6-bicyclic system through the ring contraction of compounds produced during the synthesis of isoacanthodoral (Chapter 1) are described. In an alternative synthetic approach, the Diels-Alder reaction of 2-carbomethoxy-4,4-dimethyl-2-cyclopentenone (**53**) was examined. This compound has been found to be an effective dienophile which undergoes cycloaddition with a variety of dienes to give directly the functionalized *cis*-bicyclo[4.3.0]nonane system. This approach should prove useful for the synthesis of spirodysin (**46**).



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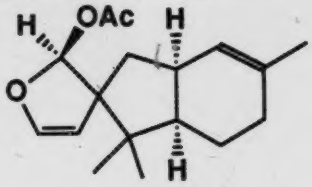

46

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Table of contents

Page

Abstract v

Acknowledgements vii

Table of Contents viii

List of Tables ix

List of Schemes x

Chapter 1. Total Synthesis of (±)-Isoacanthodoral 1

  Introduction 2

  Results and Discussion 11

  Experimental 54

Chapter 2. Towards the Synthesis of Spirodysin 92

  Introduction 93

  Results and Discussion 101

  Experimental 146

References 168

List of Tables.

Page

Table 1. Dehydration of hydroxy acetate **32** 34

Table 2. Lewis acid catalyzed Diels-Alder addition of isoprene to enone ester **53**.. 122

Table 3. Lewis acid catalyzed Diels-Alder addition of *trans*-piperylene to enone ester **53**.................................. 129

Table 4. Lewis acid catalyzed Diels-Alder addition of furan to enone ester **53** 132

Table 5. Lewis acid catalyzed Diels-Alder addition of C-1 functionalized dienes **72A** and **72B** to enone ester **53**.. 134

Table 6. Lewis acid catalyzed Diels-Alder addition of C-2 functionalized diene **73** to enone ester **53**................. 138

Table 7. Lewis acid catalyzed Diels-Alder addition of C-1 and C-3 functionalized diene **77** to enone ester **53**.. 141

List of Schemes

Page

Chapter 1

Scheme 1 7
Scheme 2 28
Scheme 3 53

Chapter 2

Scheme 4 97
Scheme 5 99
Scheme 6 118
Scheme 7 120
Scheme 8 123
Scheme 9 129
Scheme 10 130

Chapter 1

Total Synthesis of (±)-Isoacanthodoral

INTRODUCTION

In the animal world, the law of the strongest prevails. In the oceans, big fish feed on smaller fish and the smaller fish feed on smaller animals or plants. Nature uses the principle of "survival of the fittest" to control the population of animals, large or small. Interestingly, the smaller animals have developed a variety of methods to defend themselves against predators. Some species have developed erectile spines, like porcupines, while others have poisonous stinging tails, such as the scorpion. Reptiles transfer lethal chemical substances from their mouth glands into the flesh of their victims by means of a bite. There are many examples of how animals defend against predators. In our society it is known that some of these chemical defense compounds have been already used for medical purposes, since they are effective drugs in small doses.

Many examples of the survival principle are found in the food chain in the oceans. Here, animals have chosen very innovative methods of protection against predators. Some use stingers to deter enemies, for example the scorpionfish or the sea urchin, while others liberate substances that form dark clouds, like the octopus, giving them time to escape. Furthermore, many varieties of small soft-bodied animals have developed a hard outer shell as a means of protection. When there is danger present, the animal simply retracts into the shell away from the reach of the predator. The mollusc represents a good example of this type of defense system, and it is interesting to observe that in several intertidal coral areas across the globe there exist molluscs of brilliant colors, e.g. these are found in Australia's barrier reef, the Mediterranean Sea, North America's pacific coast, etc.

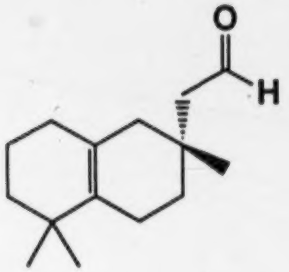
One variety of mollusc is characterized by the evolutionary loss of its shell. It has been observed that there are few predators of these animals. The question, therefore, arises: How do they protect themselves against their enemies? Some of these animals are reported to liberate organic chemicals which supposedly are of an unpleasant taste or are toxic to the predator.

In recent years, there has been an increasing interest in the chemistry and the source of the defense metabolites of the mollusc's defense mechanism. More than one of the defensive compounds have been found to be of dietary origin, while others are actually elaborated by the animal itself and stored in skin glands. When the animal is molested, it can release a charge of the "obnoxious" chemical to deter the predator.

An interesting variety of mollusc belonging to the subclass Opistobranchia, order nudibranchia, has been shown to use organic weapons, compounds that have toxic or antifeedant properties.[1] (A chemical compound is reported as an "antifeedant" when food impregnated with this substance is rejected by starved fish.) Other nudibranchs, when congregated for reproductive purposes, liberate a strong fruity odor to the environment, and this odor can be detected in areas where there is a large population of the molluscs.

Acanthodoris nanaimoensis from the suborder *Doridacea* is a colorful nudibranch found in the shallow intertidal zone of British Columbia's coast line and it is one of the nudibranchs characterized by a fruity odor. In 1984, Jocelyn T. Hellou while working with Dr. Raymond J. Andersen[2] at the University of British Columbia, showed that the odoriferous principle of this nudibranch could be extracted after the whole animals were soaked in methanol for three days. A sweet smelling oily residue was obtained in the concentrated supernatant liquid. Small quantities (150 mg / 100 animals) of the extract were obtained, thus limiting the bioassays which could be carried out. The extract was tested for antibiotic activity. It showed antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*, and antifungal activity against *Phythiam ultimum* and *Rhyzoctonia solani*. The minimum inhibitory concentration was not determined. Unfortunately, there was insufficient extract to carry out an antifeedant activity study.

Later, in the same laboratories, Stephen W. Ayer[3, 4] showed that the odor of the oily residue from *Acanthodoris nanaimoensis* was due to a mixture of aldehydes. Careful purification by repetitive standard chromatography or by preparative gas chromatography or by high performance liquid chromatography (HPLC), led to the separation of the three major components which were subsequently identified as nanaimoal (**1**, 79 %),[3] acanthodoral (**2**, 1 %) and isoacanthodoral (**3**, 20 %).[4,5]



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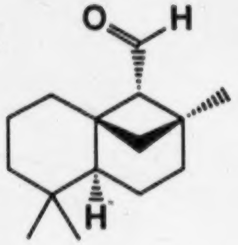

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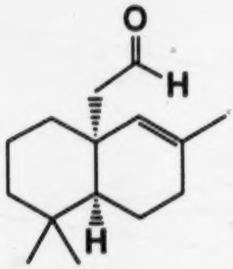

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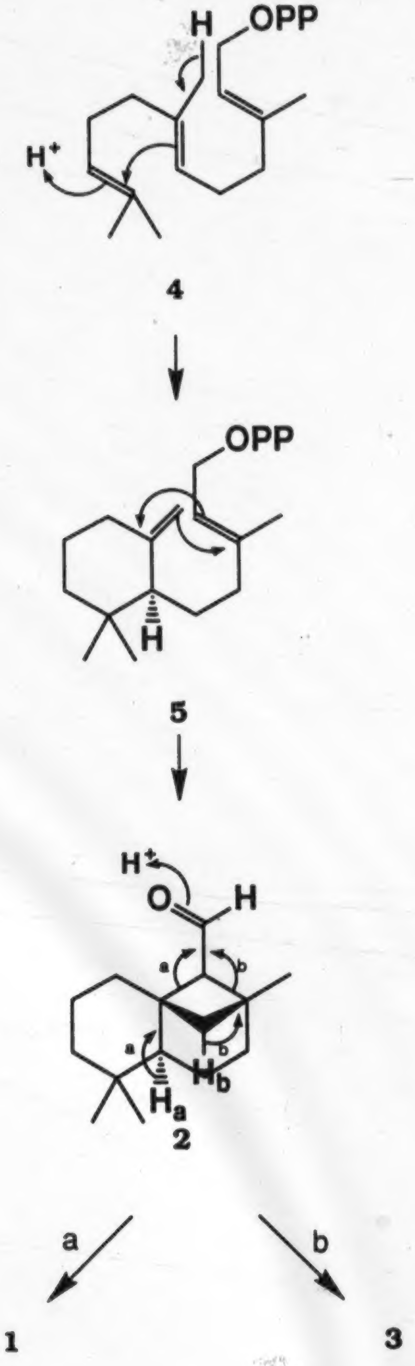
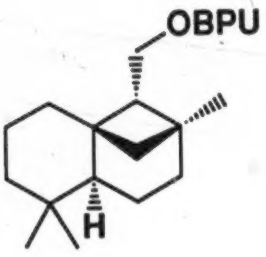
It has been suggested that the biosynthesis of isoacanthodoral does not follow the biogenetic isoprene rule.[2] It was postulated to involve a stepwise cyclization of an isoprenoid precursor such as farnesyl pyrophosphate (**4**). An acid catalyzed cyclization would lead to intermediate **5**, a monocyclofarnesane. A [2+2] cycloaddition reaction would afford the cyclobutane intermediate which would give acanthodoral (**2**), following hydrolysis and oxidation of the hydroxy group to the aldehyde. An acid induced fragmentation of the cyclobutane ring of **2** could lead to two different new structures. Removal of $\mathbf{H_a}$, and rearrangement gives nanaimoal (**1**). Removal of $\mathbf{H_b}$ and rearrangement gives isoacanthodoral (**3**).

The structure of nanaimoal (**1**),[3] a fragrant sesquiterpenoid aldehyde, was assigned based on its spectral properties and a simple synthesis of a *p*-bromophenylurethane derived from the natural product. The mixture of the naturally occurring aldehydes was subjected to reduction in isopropyl alcohol, with sodium borohydride. The mixture of alcohols was then treated with an excess of *p*-bromophenyl isocyanate in carbon tetrachloride, to give a mixture of urethanes in quantitative yield. The urethanes were separated by preparative reverse phase HPLC (15 % water/acetonitrile). The urethane derivative of nanaimoal (**1**) was synthesized by means of a Diels-Alder reaction of myrcene and 3-methyl-3-buten-1-ol. This reaction gave a mixture of alcohols, which could be separated, and converted to the corresponding *p*-bromophenylurethane derivatives. One of them was shown to be identical to the one obtained from the natural product.

Scheme 1


H
OPP
H+
4
OPP
H
5
H+
O
H
a
b
a
b
Ha
Hb
2
a
b
1
3

Acanthodoral (**2**), one of the minor aldehydes, was identified by X-ray diffraction analysis of its *p*-bromophenylurethane derivative **7**. Isoacanthodoral (**3**), was transformed to its 2,4-dinitrophenylhydrazone **8** for X-ray diffraction analysis, since its *p*-bromophenylurethane derivative was an oil.[5]



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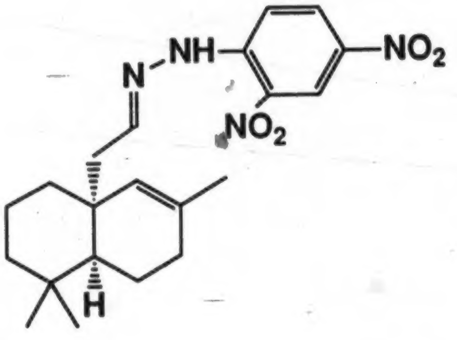

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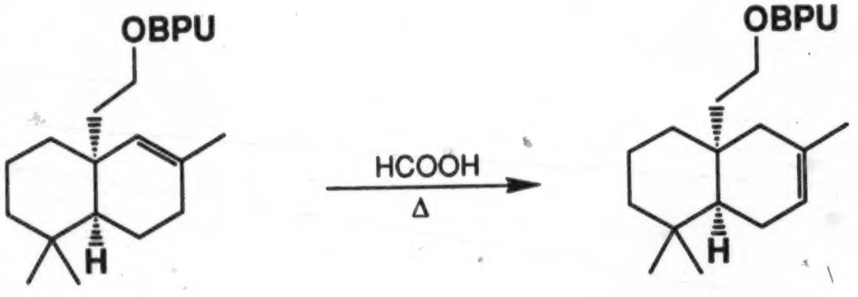
Interestingly, the *p*-bromophenylurethane derivative of isoacanthodoral, compound **6**, gave a quantitative yield of the isomeric olefin **6a** upon treatment with 98-100 % formic acid at 70°C overnight.



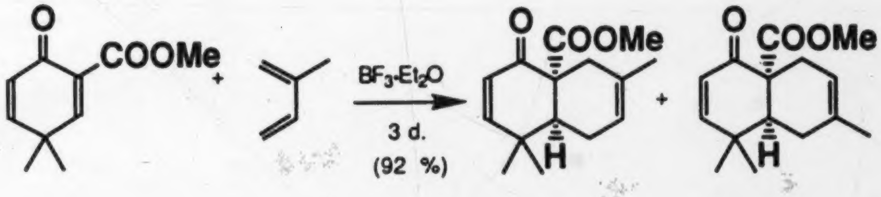
6 **6a**

Isoacanthodoral contains a *cis*-fused bicyclic structure, and is the first compound of this type reported from a nudibranch.

The optical activity of compound **3** could not be determined since it was difficult to separate from the other aldehydes. However, the rotation of its *p*-bromophenylurethane derivative **6** was observed as $[\alpha]_D$ -39° (c 0.88, hexane).

The absolute stereochemistry of nanaimoal, acanthodoral and isoacanthodoral was determined during their structure elucidation. Nanaimoane, acanthodorane and isoacanthodorane are the names proposed for the novel carbon skeletons of these three sesquiterpenoids.

In 1981, a publication on the total synthesis of α- and β-himachalene came out of this laboratory.[6] In this synthesis a Diels-Alder cycloaddition reaction between 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadienone (**12**) and isoprene in the presence of boron trifluoride etherate was employed, giving a 7:3 mixture of cycloadducts **14** and **13**, respectively. Compound **13** proved to be the useful intermediate for the synthesis of himachalenes. Interestingly, cycloadduct **14**, the major component of the mixture, is derived from an *anti-para* addition of dienophile **12** to isoprene.



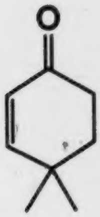
12 **14** **13**

Compound **14** is an attractive substrate which has almost the complete carbon skeleton for the synthesis of isoacanthodoral (**3**). Complete reduction of the α,β-unsaturated ketone moiety, modification of the carbomethoxy group to an aldehyde unit, and isomerization of the isolated double bond are all that is required to furnish compound **3**. A description of the total synthesis of isoacanthodoral in a racemic form on the basis of this approach constitutes the first part of this thesis. This work also serves as a proof of the structural assignment previously reported elsewhere.

Results and Discussion

As mentioned previously, compound **14** possesses most of the isoacanthodorane skeleton. This compound is prepared by a Diels-Alder reaction of 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**12**) and isoprene in the presence of boron trifluoride etherate.[6] A large quantity of dienophile **12** is necessary in order to obtain the required amount of Diels-Alder adduct **14**.

Compound **12** is derived in two steps from 4,4-dimethyl-2-cyclohexen-1-one (**9**). Compound **9** is readily available by basic[7] or acidic[8] condensation of isobutyraldehyde and methyl vinyl ketone. Subsequently, it is necessary to introduce a carbomethoxy group (**9** → **10**) and a second double bond to compound **9** to furnish dienophile **12**. Previously in this group, the formation of the double bond was performed by the oxidative elimination of selenium compounds, generated using either selenium oxide[9,10] or phenylselenenyl halides.[11,12] However, this type of elimination presented problems such as the disposal of the toxic selenium-derived products when large scale reactions were carried out and the purification of the final product which was routinely hindered by the presence of a red selenium-derived product. Thus, a different method for the introduction of the double bond was used.



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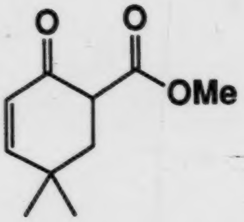

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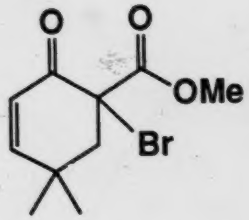
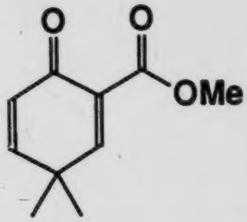


11

Reaction of the keto ester **10** with *N*-bromosuccinimide in carbon tetrachloride proceeded smoothly producing the bromo keto ester **11** in good yield (93 %). That compound **11** was formed was based upon the following observations. The spectral characteristics of compound **10** were absent in the spectra of compound **11**: no enolic hydrogen singlet was present at δ 11.77 in the ^{1}H nmr spectrum and no dienol ester carbonyl at 1685 cm^{-1} in the ir spectrum.

Compound **11** shows molecular ion peaks at 260.0034 and 262.0031 in its mass spectrum consistent with the molecular formula $C_{10}H_{13}O_3Br$. The ^{1}H nmr spectrum displays the β and α protons of the α,β-unsaturated ketone at δ 6.68 (doublet of doublets) and 6.05 (doublet), respectively. The methylene protons at C-5 appear at δ 3.03 (doublet of doublets, J = 14, J' = 2 Hz) and 2.53 (doublet, J = 14 Hz). The proton at δ 3.03 shows a four-bond coupling to the proton at C-3. There are three methyl singlets at δ 3.82 (ester), 1.28 and 1.13 (*gem*-dimethyl) in the ^{1}H nmr spectrum.

Further evidence for the structure of compound **11** was provided by its ^{13}C nmr APT spectrum. It shows the presence of signals consistent with the α,β-unsaturated ketone (δ 187.7 (ketone carbonyl), 158.5 (β-carbon) and 124.1 (α-carbon)). Signals characteristic of an ester carbonyl (δ 169.0) and a quaternary carbon bearing a bromine atom and two electron withdrawing groups (δ 61.9) are also present in the spectrum.



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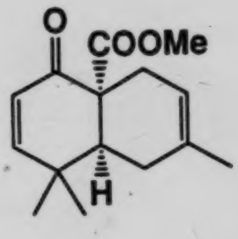
Elimination of hydrogen bromide from **11** was performed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene[13] in benzene at room temperature to give an oil. The ^{1}H nmr spectrum of the product (78 % yield) shows three sets of peaks corresponding to the C-3, C-5 and the C-6 protons, at δ 7.35 (doublet, $J = 3$ Hz), 6.83 (doublet of doublets, $J = 10$, $J' = 3$ Hz), and 6.10 (doublet, $J = 10$ Hz),. respectively. The two β-hydrogens (H-3 and H-5) show a four-bond coupling ($J = 3$ Hz). A 3 H-singlet at δ 3.75 confirms the presence of the carbomethoxyl group in the molecule, while a 6-H singlet (δ 1.35) shows the *gem*-dimethyl group. The molecular ion peak at m/z 180.0784 is consistent with the anticipated molecular formula of $C_{10}H_{12}O_3$. Thus, compound **12** could be produced in the required quantities more conveniently by this new method.



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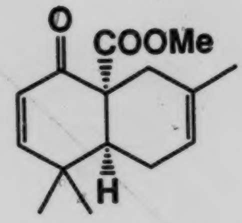


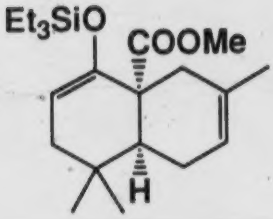
14

Another problem that had to be surmounted was the separation of the isomeric keto esters **13** and **14** (ratio 3 : 7) produced by the Diels-Alder reaction between the dienophile **12** and isoprene. Previously, the isomers were separated by preparative high pressure liquid chromatography.[2, 14] This was a tedious process since the two compounds were barely separable in the column, and pure compounds could be obtained only by cutting the heads and tails of the single peak in the chromatogram. The bulk of the mixture recovered was recycled through the column for further separation. Although this technique effected partial separation of the two isomers, the small quantities of pure material obtained, combined with the time and solvent invested in the separation, made this technique impractical. Nevertheless, small amounts of pure keto esters **13** and **14** were obtained by this process.

Several other methods were investigated for the separation of the isomeric compounds **13** and **14**. Silver nitrate impregnated on chromatographic supports has given good separation of olefins.[15,16] Unfortunately, all attempts to separate compounds **13** and **14** failed when different concentrations of silver nitrate on silica gel were employed.

A more successful procedure for the separation of the two isomeric **13** and **14** was accomplished by fractional crystallization. Seeding an ether solution of the mixture with pure keto ester **14** induced the formation of crystals which were shown to consist mainly of the major isomer. Further recrystallizations from ether gave pure compound **14**.

Although an approximate 40 % of pure compound **14** could be separated from the 30 : 70 mixture of isomers **13** and **14**, the rest of compound **14** remained in the mixture and could not be further separated by fractional crystallization. Later on in the synthesis, when a method for the separation of the isomeric compounds was in hand, this residual mixture became very useful.



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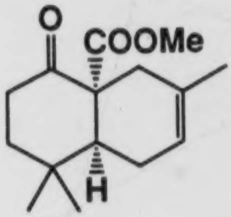

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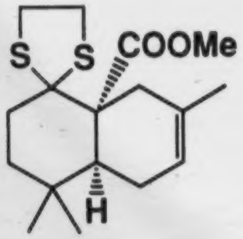
With pure keto ester **14** in hand, the construction of the isoacanthodorane carbon framework was almost complete. It remained to modify the existing functional groups. First of all the enone moiety in the "A-ring" had to be reduced to the hydrocarbon level. Hydrogenation[17, 18] was unlikely to meet with success because of the presence of the isolated double bond in the "B-ring". Birch-type reduction[19] was not appropriate since the use of Li or Na in an amine could induce decarbomethoxylation of the ester group α to the ketone.[20] However, hydrosilylation may be a useful method. The reaction can be effected by the use of tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst) and trialkylsilanes.[6, 21] Treatment of compound **14** with triethylsilane in the presence of Wilkinson's catalyst gave the triethyl silyl enol ether **15** in excellent yield (97 %). Compound **15** shows two vinylic protons in the ^{1}H nmr spectrum, one for the C-8 proton (broad singlet, δ 5.35) and another for the C-3 proton (dd, δ 4.67, *J* = 6, *J'* = 2 Hz) which is coupled to both methylene protons at C-4.

The presence of four peaks in the ^{13}C nmr APT spectrum, two singlets (δ 151.0 and 131.9) and two doublets (δ 118.8 and 99.1), confirms the presence of two trisubstituted double bonds. The molecular ion peak at m/z 364.2440 supports the formula $C_{21}H_{36}O_3Si$.

Hydrolysis of the silyl enol ether **15** with aqueous potassium bicarbonate in methanol gave crystalline ketone **16** in 100 % yield. The ^{1}H nmr spectrum of compound **16** shows a broad singlet at δ 5.32 for the vinylic hydrogen. The infrared spectrum shows two carbonyl absorptions at 1743 (ester) and 1711 cm^{-1} (ketone). The molecular peak at m/z 150.1569 supports the molecular formula $C_{15}H_{22}O_3$.



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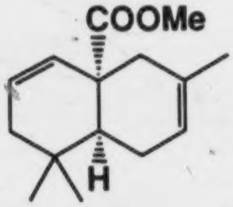
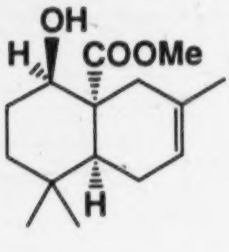


18

Decarboxylation of β-keto esters[22] may occur under acidic or basic conditions to give a saturated ketone. Wolff-Kishner[23] and the Clemmensen[24] reductions employ harsh conditions, making these methods unsuitable for the required removal of the ketone carbonyl. Earlier in these laboratories, Lloyd A. K. Nelson[25] treated keto ester **16** with 1,2-ethanedithiol in the presence of boron trifluoride etherate to generate the thioacetal **17**. Upon Raney Nickel reduction, compounds **24** and **18** were obtained in a 1 : 1 ratio and an overall yield of 80 %. This meant that the desired ester **24** was produced in only 40 % yield.



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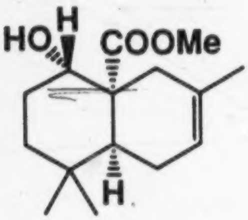


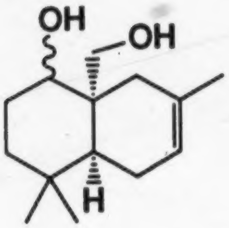
20

An improved route to compound **24** employed the stepwise reduction of the ketone carbonyl, first to the alcohol level and then deoxygenation. Thus, keto ester **16** was dissolved in methanol and cooled to -40°C. Slow addition of sodium borohydride to the solution and a short reaction time (15 min) gave 95 % of a mixture of epimeric alcohols (**19** : **20**) in a 5 : 1 ratio.

The major alcohol (**19**) has strong absorptions in the ir spectrum at 3470 (alcohol) and 1737 cm^{-1} (ester). In the ^1H nmr spectrum, the vinylic proton appears at δ 5.27 as a broad singlet. The C-2 proton is displayed at δ 3.90 as a doublet of doublets of doublets with coupling constant of 9, 7 and 4 Hz. The small coupling constant of 4 Hz is due to the coupling with the hydroxy proton which appears at δ 1.88 as a doublet. Four methyl singlets are observed at δ 3.72 (ester), 1.68 (vinylic), 0.94 and 0.83 (*gem*-dimethyl). The infrared spectrum of the minor isomer **20** shows strong absorptions at 3529 (alcohol) and 1739 cm^{-1} (ester). Its ^1H nmr spectrum displays the vinylic proton at δ 5.35 as a broad singlet. The proton attached to C-2 appears at δ 3.60 (ddd, $J = 10$, $J' = 7$, $J'' = 7$ Hz) coupled to the hydroxy proton at δ 3.06. Four singlets are observed at δ 3.70 (ester), 1.66 (vinylic), 0.96 and 0.89 (*gem*-dimethyl).

The stereochemistry of alcohols **19** and **20** at C-2 was proven by the following nOe experiments. Irradiation of the proton at C-2 (δ 3.90) in the major isomer **19** gave an 8 % nOe enhancement of the signal at δ 1.93, attributed to the bridgehead proton at C-6. On the other hand irradiation of the C-2 proton (δ 3.60) in the minor isomer **20** gave no enhancement of the signal at δ 2.30-2.15.

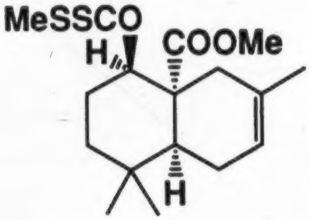
Isomerization of cyclic β-hydroxy carbonyl compounds may take place through a retro-aldol type process,[26] involving opening and reclosing of the ring, resulting in the formation of stereoisomers.[27] In order to ascertain that the stereochemistry of the C-1 center remained intact during the reduction of keto ester **16**, compounds **19** and **20** were individually treated with sodium hydride in dimethoxyethane, at room temperature for 12 h. In each case, the starting material was recovered unchanged.



21

It is noteworthy that in the reduction of **16**, higher temperature or longer reaction time led to the production of the over-reduced product **21**. The reduction of the ester moiety is thought to proceed through a four-membered ring lactone, formed after the initial reduction of the ketone carbonyl, or through an intramolecular hydride transfer from the boron-C-2 oxygen complex formed after the first reduction. Diol **21** shows a broad absorption in the infrared spectrum at 3290 cm^{-1} indicating the presence of an hydroxy group. The ^{1}H nmr spectrum displays a broad singlet at δ 5.22 for the vinylic proton. The hydroxy protons appear at δ 4.51 and 3.22, which disappear upon addition of D_2O. A doublet of doublets at δ 3.65 (J = 12, J' = 4 Hz) was assigned to the C-2 proton. The methylene protons of the hydroxymethyl group are displayed at δ 3.53 and 3.26 as a AB system with a coupling constant of 10 Hz. Three methyl singlets are observed at δ 1.54 (vinylic), 0.82 and 0.75 (*gem*-dimethyl). High resolution mass spectrometry shows a molecular ion peak at m/z 224.1774, in agreement with the assigned molecular formula $C_{14}H_{24}O_2$.

Deoxygenation of an alcohol can be performed in a number of ways, e.g. via the reduction of the corresponding ester,[28] xanthate[29] or sulfonate.[30] For our purpose, the use of a strong reducing agent such as lithium aluminium hydride should be avoided because of the presence of the ester moiety in the molecule. For the removal of the hydroxy group present in compounds **19** and **20** the corresponding xanthates were prepared. The reduction of xanthates requires tri-*n*-butyltin hydride.



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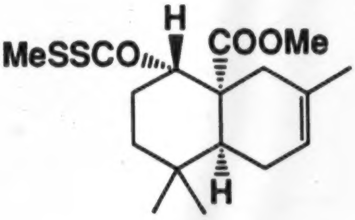


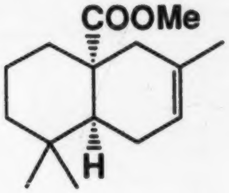
23

Thus, each of the hydroxy esters **19** and **20** was treated with sodium hydride in 1,2-dimethoxyethane to give the corresponding sodium alkoxide, followed by reaction with carbon disulfide to generate the sodium xanthate. The salt was alkylated *in situ* with methyl iodide to produce the corresponding methyl xanthate.

Compound **22**, obtained from hydroxy ester **19**, has strong absorptions in its infrared spectrum at 1737 (ester) and 1240 cm^{-1} (xanthate). In the ^{1}H nmr spectrum the C-10 proton appears at δ 5.96 (dd, *J* = 11.5, *J'* = 4.5 Hz), while the vinylic proton is displayed at δ 5.26 as a broad singlet. Five methyl singlets are also observed at δ 3.62 (ester), 2.52 (xanthate), 1.69 (vinylic), 0.96 and 0.87 (geminal methyls).

The infrared spectrum of xanthate **23** has bands at 1738 (ester) and 1232 cm^{-1} (xanthate). In the ^{1}H nmr spectrum, the proton at C-10 appears at δ 5.74 as a doublet of doublets (*J* = *J'* = 3 Hz), and the vinylic proton is shown as a broad singlet at δ 5.28. Five methyl singlets are displayed at δ 3.55 (ester), 2.50 (xanthate), 1.54 (vinylic), 0.96 and 0.81 (geminal).

The stereochemistry of the xanthates epimeric at C-10 was confirmed by comparing the ^{1}H nmr chemical shifts and the coupling constants observed for the C-10 protons. In compound **22** the proton at C-10 is a doublet of doublets with a large coupling constant of 11.5 Hz and a small coupling constant of 4.5 Hz, indicating its axial orientation. In contrast, xanthate **23** shows a doublet of doublets with two small coupling constants of 3 Hz each for the C-10 proton, indicating its equatorial orientation. These stereochemical assignments were further substantiated by the following nOe experiment. When the C-6 hydrogen (δ 1.98-2.06) of compound **22** was irradiated, the C-10 proton (δ 5.96) signal showed a large enhancement of 11.2 %. Thus, the C-10 and C-6 hydrogens in xanthate **22** are *cis* to each other. In contrast, when the C-6 hydrogen (δ 2.06) of compound **23** was irradiated, the C-10 signal (δ 5.74) remained unchanged.



24

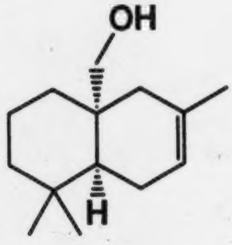
The reduction of xanthates **22** and **23** in pure form or as a mixture with tri-*n*-butyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile[29] afforded ester **24** virtually in quantitative yield. The infrared spectrum of ester **24** shows a strong absorption at 1730 cm^{-1} (ester). In the ^1H nmr spectrum a vinylic proton appears at δ 5.30 as a broad singlet. The rest of the spectrum is rather complex, except for the four distinct methyl singlets at δ 3.68 (ester), 1.64 (vinylic), 0.96 and 0.88 (*gem*-dimethyl). The molecular ion peak at m/z 236.1780 is in accordance with the molecular formula $C_{15}H_{24}O_2$.

Having successfully removed the unnecessary functionalities from "ring-A", it remained to carry out the following transformations in order to complete the synthesis of isoacanthodoral. The ester group in compound **24** must be converted to an acetaldehyde unit and the double bond must be moved to the adjacent position. We chose to modify the ester group first.

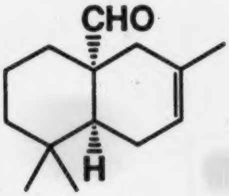
Homologation by one carbon unit can be carried out in a number of ways.[31-37] A frequently used procedure involves the

Wittig reaction[36, 37] of an aldehyde with (methoxymethyl)-triphenylphosphorane, followed by hydrolysis of the resulting enol ethers.

Several attempts were made to reduce ester **24** directly to aldehyde **27**. When ester **24** was treated with diisobutylaluminum hydride[25] in toluene at -78°C, reduction did not take place. When the reaction was carried out at room temperature, only a 20 % yield of the desired aldehyde was obtained. This aldehyde was produced more effectively by a two step sequence as follows.



26



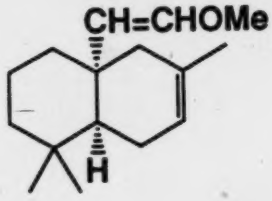
27

Treatment of ester **24** with lithium aluminum hydride in dry ether gave the alcohol **26** as a crystalline solid in 96 % yield. The existence of the hydroxy group was confirmed by the presence of a broad band at 3280 cm^{-1} in the infrared spectrum. Its ^{1}H nmr spectrum displays an AB system at δ 3.39 (d, J = 10 Hz) and 3.27 (d, J = 10 Hz). The vinylic proton appears as a broad singlet at δ 5.29. The methyl singlets are shown at δ 1.62 (vinylic), 0.94 and 0.84 (*gem*-dimethyl). The molecular ion peak at m/z 208.1833 is consistent with the molecular formula $C_{14}H_{24}O$.

Swern oxidation[38, 39] is a preferred method for the oxidation of a primary alcohol to an aldehyde because there is no danger of overoxidation to the carboxylic acid. When treated under Swern oxidation conditions alcohol **26** gave aldehyde **27** in 80 % yield. Unfortunately, compound **27** proved to be quite volatile, making its isolation rather difficult.

Another good method for the conversion of alcohols to the corresponding aldehydes involves the use of pyridinium chlorochromate on alumina.[40] This method is specially useful when the product is unstable or volatile. The reaction is generally carried out with a suspension of the reagent in dichloromethane, and when the reaction is over a simple filtration makes the isolation of the product rather convenient. Treatment of alcohol **26** with pyridinium chlorochromate on alumina in dichloromethane at room temperature for 2 h gave an 88 % yield of aldehyde **27**, which did not require further purification. Mass spectrometry gave a molecular ion peak at m/z 206.1673 which confirmed a molecular formula $C_{14}H_{22}O$ for compound **27**. The infrared spectrum of compound **27** shows three characteristic aldehydic absorption bands at 2840, 2700 and 1724 cm^{-1}. The ^1H nmr spectrum displays an aldehyde hydrogen at δ 9.32 (singlet) and a vinylic hydrogen at δ 5.32 (broad singlet). Three methyl singlets are present at δ 1.67

(vinylic), 0.96 and 0.86 (*gem*-dimethyl). In the ^{13}C nmr APT spectrum a carbonyl signal at δ 205.6 in antiphase with the deuteriochloroform signal, provided further evidence for the presence of an aldehyde moiety in the molecule.

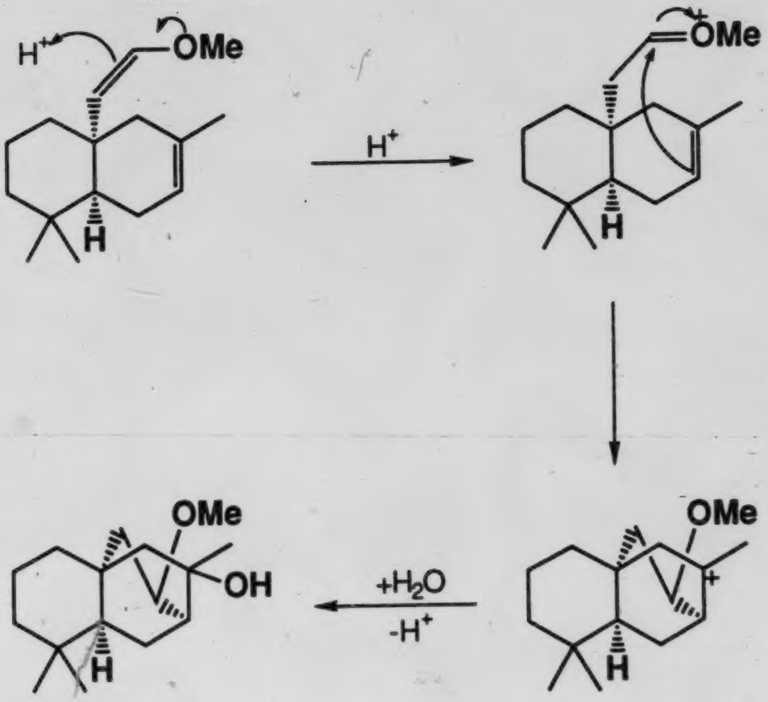


28

Addition of aldehyde **27** to a deep red benzene solution of (methoxymethyl)triphenylphosphorane gave a 1 : 1 mixture of *cis* and *trans* enol ethers **28** in 98 % yield. The ^1H nmr spectrum of the unseparable mixture displays an AX system at δ 6.18 and 4.77 with a *trans* coupling constant of 13 Hz, and an AM system at δ 5.63 and 4.17 with a coupling constant of 7.5 Hz. These signals were assigned to the vinylic protons of the enol ether moiety. The signal at lower field in each pair (δ 6.18 and 5.63) is due to the proton attached to the carbon bearing the methoxy group. The signal at the higher field in each case (δ 5.66 and 4.24) corresponds to the proton β to the methoxy group. The mixture also shows methoxy singlets at δ 3.52 and 3.48, a broad singlet at δ 1.61 for the vinylic methyl groups, and four methyl singlets at δ 0.97, 0.90, 0.83 and 0.81 (*gem*-dimethyl). The infrared spectrum displays absorption bands at 1651 (double bond) and 1205 cm^{-1} (ether). The mass spectrum of the mixture shows the molecular ion peak at m/z 234.1984 in accordance with the molecular formula $C_{16}H_{26}O$.

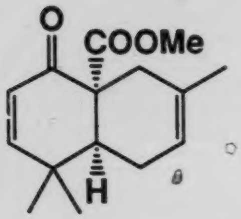
Attempts to hydrolyze the enol ethers **28** under acidic conditions led to complete decomposition of the material. The desired aldehyde was not formed. Nelson[25] reported the attempted hydrolysis of enol ethers **28** by the use of different demethylating agents such as chlorotrimethylsilane and sodium iodide in acetonitrile,[41] phenyl dichlorophosphate and sodium iodide[42] and sodium ethylthiolate.[43] In all the cases, the starting material was recovered intact. Nelson also reported the isolation of a product when enol ethers **28** were subjected to acid treatment. This compound showed a strong hydroxy absorption at 3400 cm^{-1} in the infrared spectrum. The ^1H nmr spectrum of this compound displayed a methine hydrogen at δ 4.60 as a multiplet. The mass spectrum gave a molecular ion peak at m/z 250.1932 corresponding to a molecular formula $C_{16}H_{26}O_2$. These spectral data are consistent with structure **29**. This compound may arise from a Prins-type reaction as shown in Scheme 2.

Scheme 2



29

In the present studies, a vinyl transetherification reaction catalyzed by mercury(II) salts[44, 45] was also attempted. Mercury(II) nitrate was added to a solution of the enol ethers **28** in acetonitrile - water (5 : 1). After 2 h at room temperature, the starting material was completely consumed. Unfortunately, no identifiable products were isolated. Further attempts to hydrolyze enol ethers **28** were abandoned.



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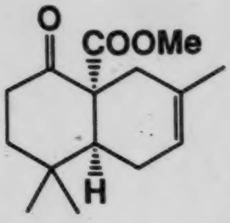
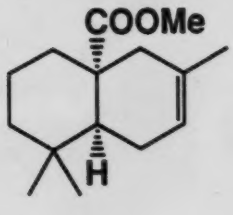
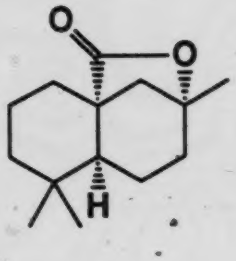


16

In reassessing the synthetic strategy it was deemed appropriate to move the existing endocyclic double bond first, since most of the difficulties encounter were related to this double bond. Direct isomerization of the double bond was attempted. α,β-Unsaturated keto ester **14** was dissolved in carbon tetrachloride and refluxed overnight in the presence of trifluoroacetic acid. Only starting material was recovered. Under the same conditions, keto ester **16** was also recovered intact. At this point, it was apparent that the direct isomerization of the double bond was not feasible. Therefore, a functional group must be introduced to the disubstituted end of the double bond following by elimination.



24



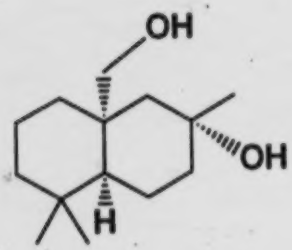
30

Ester **24** has only two functional groups, making it a good candidate for the introduction of the required functional group. Treatment of ester **24** in hexane saturated with hydrogen bromide or hydrogen chloride gas at room temperature gave a crystalline product which did not contain any halogen atoms. Apparently hydrohalogenation had not taken place. The infrared spectrum of the product shows a strong absorption at 1753 cm^{-1}, which indicated the presence of a carbonyl group. However, this was not a typical absorption for an ester. The ^1H nmr spectrum confirmed the absence of the ester group and the double bond. Mass spectrometry gave a molecular ion peak at m/z 222.1619 in accordance with a molecular formula $C_{14}H_{22}O_2$. Further evidence to support this molecular formula was provided by the ^{13}C nmr spectrum showing 14 signals and the elemental analysis (C; 75.62 %, H 9.98 %) indicating the presence of 22 hydrogens. These spectroscopic data are consistent with structure **30**. When ester **24** was treated with *p*-toluenesulfonic acid in refluxing benzene, lactone **30** was also obtained in 90 % yield.

Compound **30** would arise if the double bond of compound **24** is protonated and the incipient tertiary carbocation is attacked intramolecularly by the carbonyl oxygen rather than by the external nucleophile (halogen). Although it was not possible to introduce a halogen to the double bond, an oxygen atom was efficiently incorporated. This would also allow for the subsequent regeneration of a double bond, hopefully at the required position. In order to do so, it was necessary to open the lactone ring to a hydroxy ester. The combination of sodium methoxide-methanol, sodium ethoxide-ethanol and sodium isopropoxide-isopropyl alcohol were used in attempts to cleave the lactone ring in compound **30**. Examination of the reaction in each case by tlc showed that the starting material had been consumed during the reaction but the lactone was regenerated upon addition of water and the desired product could not be isolated.

Since we were unable to hydrolyze the lactone, it was decided to reduce it completely to a diol. Thus, lactone **30** was treated with lithium aluminum hydride in ether and diol **31** was formed in 97 % yield. A broad alcohol absorption at 3349 cm^{-1} was present in the infrared spectrum of the product. The ^1H nmr spectrum was complex, with the exception of an AB system at δ 3.98 (d, $J = 11$ Hz) and 3.14 (d, $J = 11$ Hz) due to the methylene protons adjacent to the hydroxy group, and the three methyl singlets at δ 1.23 (vinylic), 0.98 and 0.95 (*gem*-dimethyl). The ^{13}C nmr APT spectrum displays signals for two oxygen-bearing carbons at δ 74.1 and 70.6. The molecular ion peak at m/z 226.1924 is consistent with the molecular formula $C_{14}H_{26}O_2$.

At this point, it was necessary to decide whether to introduce the double bond or to extend the side chain first. In an unsuccessful attempt to extend the angular chain, the primary alcohol was oxidized with PCC on Al_2O_3. The unstable hydroxy aldehyde thus obtained, was immediately subjected to a Wittig reaction with (methoxymethyl)triphenylphosphorane. Complete decomposition of the starting aldehyde ocurred without apparent formation of the desired product. These results prompted us to undertake the other approach, i.e. regeneration of the double bond before extension of the angular chain.



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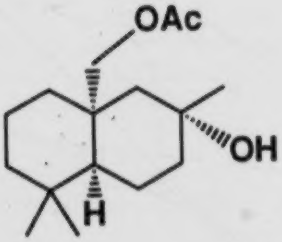


32

To avoid problems during the dehydration reaction, it was deemed necessary to protect the primary alcohol first. Selective protection was readily achieved as follows. Freshly distilled acetic anhydride was added to a solution of diol **31** in dry pyridine. After an overnight reaction period at room temperature, hydroxy acetate **32** was isolated as a colorless oil in 90 % yield. The infrared spectrum of compound **32** displays a broad alcohol band at 3480 cm^{-1} and intense acetate carbonyl absorptions at 1737 and 1720 cm^{-1}. In the ^{1}H nmr spectrum, the methylene protons neighboring the acetate moiety appear as an AB system at δ 4.31 (d, J = 11 Hz) and 4.14 (d, J = 11 Hz). Four methyl singlets are displayed at δ 2.07 (acetate), 1.22

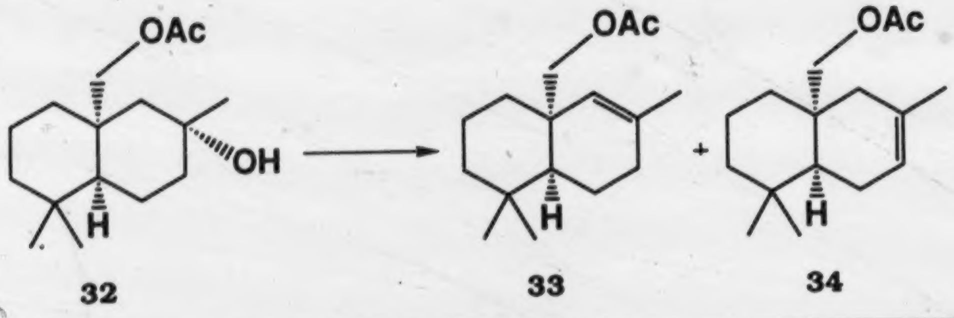
(vinylic), 0.98 and 0.97 (*gem*-dimethyl). The ^{13}C nmr APT spectrum shows the carbonyl at δ 171.4. High resolution mass spectrometry gave a molecular ion peak at m/z 268.2033, consistent with the molecular formula $C_{16}H_{28}O_3$.

Several methods were examined for the dehydration of hydroxy acetate **32** including the use of $CuSO_4/SiO_2$,[46-48] $SOCl_2$/Py,[49] and $POCl_3$/Py-DMAP.[50] A mixture of isomeric olefins was always obtained. The results are given in Table **1**.

As can be seen from Table **1**, the dehydration reaction with copper(II) sulfate impregnated on silica in refluxing benzene (Entry 1) gave predominantly the undesirable acetate **34**. No change in the product ratio was observed when benzene was replaced with toluene. When xylenes were used, complete decomposition occurred. In contrast, when the dehydration was carried out in refluxing ether, no reaction took place.

Thionyl chloride in pyridine gave a mixture of olefins **33** and **34** in equal amounts, when the reaction was carried out at room temperature (Entry 2). When the temperature was decreased to 5°C (Entry 3), the rate of reaction decreased as expected but the product ratio remained the same.

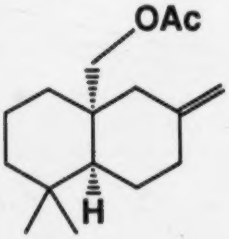
Table 1. Dehydration of hydroxy acetate **32**.



Entry	Reagent (eq.)	Solv.	DMAP (eq.)	T(°C)	Time (h)	Yield (%)	Ratio **33 : 34**
1	$CuSO_4$(1)	PhH	-	78	0.5	94	1.0 : 9.0
2	$SOCl_2$(20)	Py	-	20	1	88	1.0 : 1.0
3	$SOCl_2$(20)	Py	-	5	4	80	1.0 : 1.0
4	$POCl_3$(2)	Py	-	20	12	-	1.0 : 0.8
5	$POCl_3$(2)	Py	-	5	24	81	1.0 : 1.0
6	$POCl_3$(10)	Py	-	-30	72	86	1.1 : 1.0
7	$POCl_3$(10)	Py	1	0	21	74	0.9 : 1.0
8	$POCl_3$(10)	Py	2	-15	39	98	1.1 : 1.0
9	$POCl_3$(10)	Py	2.7	-30	72	99	1.5 : 1.0
10	$POCl_3$(10)	Py	10	-52	24	96	1.4 : 1.0
11	$POCl_3$(20)	Py	10	-62	16	97	1.4 : 1.0
12	$POCl_3$(10)	Py	5	-40	12	95	3.0 : 1.0

Similar results were obtained with phosphorus oxychloride in pyridine at a temperature range of -30°C to 20°C

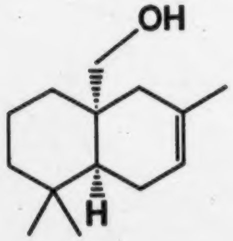
(Entries 4-6). With the aid of 4-dimethylaminopyridine (DMAP) however the formation of the desired isomer **33** was enhanced at the expense of **34**. It appears that preferential formation of **33** is highly dependent upon the ratio of the reagents and the reaction temperature (Entry 7-12). The best results were obtained when the reaction was carried out at -40°C in pyridine using 10 eq of phosphorous oxychloride and 5 eq of DMAP (Entry 12). Under these conditions a 3 : 1 mixture of acetates **33** and **34** was obtained in virtually quantitative yield.



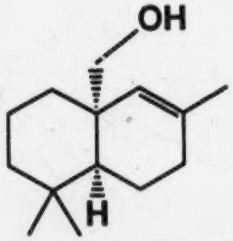
34 b

It is noteworthy that in virtually all the cases examined a very small amount (<4 % by nmr) of the exocyclic olefin **34 b** was also produced. However, all attempts to isolate this compound **34 b** by chromatography were unsuccessful, probably due to isomerization of the double bond to the more stable endocyclic position on silica gel. The presence of acetate **34 b** was indicated by the ^{1}H nmr spectrum of the mixture showing two broad doublets at δ 4.69 and 4.57 (J = 1 Hz each) due to the exocyclic methylene hydrogen atoms.

Isomeric olefins **33** and **34** were found to be inseparable. For characterization purposes, compound **34** was produced via a completely different route. Alcohol **26**, obtained from the lithium aluminum hydride reduction of ester **24**, was acetylated with acetic anhydride in pyridine. The ^{1}H nmr spectrum of compound **34** thus obtained in quantitative yield, shows a vinylic hydrogen at δ 5.28 (broad singlet), as well as two methylene hydrogens adjacent to a acetyl group at δ 3.96 (d, J = 10.5 Hz) and 3.78 (d, J = 10.5 Hz). Four methyl singlets are observed at δ 2.08 (ester), 1.62 (vinylic), 0.92 and 0.83 (*gem*-dimethyl). The infrared spectrum shows strong absorptions attributed to the acetate at 1742 (C=O) and 1235 cm^{-1} (C-O). No bands above 3000 cm^{-1} are observed confirming the absence of hydroxy group. The required molecular ion peak at m/z 250.1930 was obtained.



26

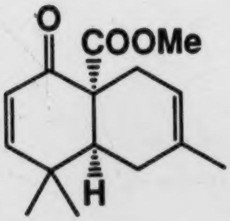


35

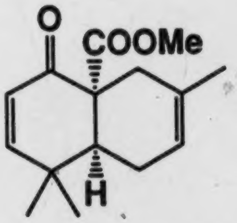
The mixture of acetates **33** and **34** was hydrolyzed with an aqueous solution of potassium carbonate in methanol. After refluxing for 2.5 h a mixture of hydroxy olefins was obtained in 98 % yield. Separation of alcohols **26** and **35** was achieved by flash chromatography on silica gel. The spectroscopic characteristics of alcohol **26**, obtained in 22 % yield, have been described previously in this thesis. Alcohol **35** was obtained as a colorless oil in 70 % yield. The infrared spectrum shows an alcohol absorption at 3256 cm^{-1}. Its ^{1}H nmr spectrum displays a vinylic hydrogen as a broad singlet at δ 5.01. An AB system is observed at δ 3.43 (d, J = 11 Hz) and 3.27 (d, J = 11 Hz). These signals were readily assigned to the methylene unit of the hydroxymethyl chain. Methyl singlets are displayed at δ 1.75 (vinylic), 1.00 and 0.91 (*gem*-dimethyl). The ^{13}C nmr APT spectrum displays two signals at δ 137.6 and 128.3, confirming the presence of a trisubstituted double bond. It is noteworthy that signals of the olefinic carbons of **26** occurred at a higher field of δ 131.6 and 119.7. High resolution mass spectrometry of alcohol **35** provided a molecular ion peak at m/z 208.1827, consistent with the molecular formula $C_{14}H_{24}O$.

The studies on the dehydration of hydroxy acetate **32** depleted our stock of this material. It was necessary to prepare more Diels-Alder adducts, to separate isomer **14** required for the synthesis and then to repeat the reaction sequence leading to alcohol **35**. At this point, a literature search was carried out in order to find a simpler approach, which would allow for a more rapid reduction of the enone system present in adduct **14**.

It has been reported that ionic hydrogenation[51-54] can be performed using trialkylsilanes and a strong acid or boron trifluoride.[55] Trisubstituted and tetrasubstituted olefins are reduced to the saturated hydrocarbons. Aldehydes and ketones are reduced to the alcohols or to the saturated hydrocarbons. The degree of reduction depends on the ratio of the reducing agent and acid used and on the nature of the carbonyl group. When the carbonyl group is conjugated to an aromatic ring, reduction to the hydrocarbon level takes place. Mixtures of epimeric alcohols and trifluoroacetate esters are obtained when aliphatic ketones are reacted with triethylsilane in the presence of trifluoroacetic acid. An α,β-unsaturated ketone can also be reduced to the saturated ketone or alcohol, depending on the quantities of the acid and the reducing agent used. Therefore, ionic hydrogenation presented itself as a good option for the reduction of the α,β-unsaturated ketone group in compound **14**.



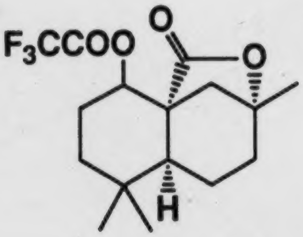
13



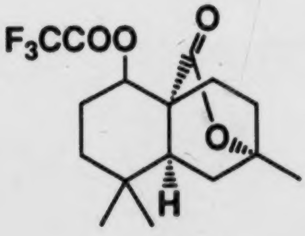
14

By this time, a fair amount of keto esters **13** and **14** in mixture form had been accumulated. These were used to study the selective reduction of the enone system to the saturated ketone using the ionic hydrogenation conditions described by Kurzanov.[53] When a mixture of **13** and **14** was treated with triethylsilane and trifluoroacetic acid, in a ratio of 1:1:10 respectively, in refluxing carbon tetrachloride only partial reduction was observed. A variety of reduction products was obtained along with unreacted starting material. The reaction was repeated several times using different temperatures and reaction times. Invariably, a complex mixture was formed.

In the same paper,[53] Kurzanov also reported the direct reduction of an α,β-unsaturated ketone to the corresponding alcohol by the use of a higher concentration of triethylsilane. When the mixture of keto esters **13** and **14** was treated with 3 eq of triethylsilane and 10 eq of trifluoroacetic acid in refluxing carbon tetrachloride, the starting material was consumed in 9 h and a mixture of products was obtained. The complete separation of these products proved to be difficult. Nevertheless, a combination of crystallization and flash chromatography allowed for the separation of four major compounds **39-42**.

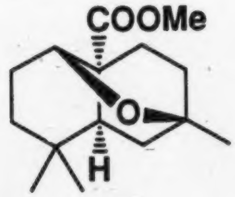


39

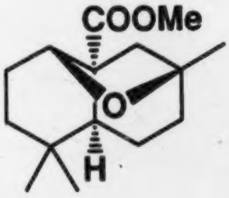


40

Trifluoroacetate lactone **39** (65 %) and ether **42** (29 %) were produced in 94 % yield from keto ester **14**, while trifluoroacetate lactone **40** (30 %) and ether **41** (36 %) were obtained in 66 % yield from keto ester **13**. There was a small fluctuation of the ratio of each pair of the products in different experiments. However the yield of each pair was rather reproducible.



41



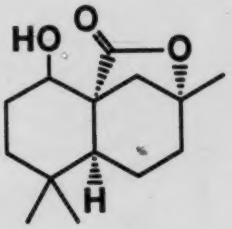
42

Ester **39** could be purified directly by crystallization from a petroleum ether solution of the reaction mixture. Recrystallization from the same solvent gave a white solid with a melting point of 132-133°C. The infrared spectrum of compound **39** shows ester absorption at 1789 cm^{-1} and lactone absorption at 1770 cm^{-1}. The ^{1}H nmr spectrum of ester **39** displays the C-8 hydrogen at δ 5.22 (dd, J = 11, J' = 4 Hz). Three methyl singlets are observed at δ 1.52 (C-1 methyl), 1.07 and 0.98 (*gem*-dimethyl). The ^{13}C nmr spectrum of compound **39** displays carbonyl signals at δ 177.1 (lactone) and 118.7 (ester). This ester signal appears at a much higher field than the standard ones (~δ 165-180) due to the inductive effect of the fluorine atoms. The high resolution mass spectrum gives a molecular ion peak at m/z 334.1390 which supports the molecular formula $C_{16}H_{21}F_{3}O_{4}$.

Sometimes the trifluoroacetate lactone **40** crystallized from the products mixture together with the isomeric lactone **39**. At other times it remained in the mother liquor until the separation by flash chromatography was carried out. Ester lactone **40** displays strong carbonyl absorption bands in the infrared spectrum at 1784 (ester) and 1739 cm^{-1} (lactone). In the ^{1}H nmr spectrum the C-8 hydrogen is displayed at δ 5.42 (dd, $J = 12$, $J' = 5$ Hz). Three methyl singlets appear at δ 1.44 (C-1 methyl), 1.09 and 0.89 (*gem*-dimethyl). The ^{13}C nmr APT spectrum shows carbonyl signals at δ 175.1 (lactone) and 116.5 (ester), together with a signal at δ 112.7 for the carbon bearing three fluoride atoms. High resolution mass spectrometry provided a molecular ion peak at m/z 334.1390, consistent with the molecular formula $C_{16}H_{21}F_{3}O_{4}$. The stereochemistry at C-8 in the trifluoroacetate esters **39** and **40** could not be unambiguously assigned. A nOe experiment on ester **39** including irradiation of the C-8 hydrogen did not produce any conclusive evidence.

Ester **41** gives absorption bands in the infrared spectrum at 1729 (ester) and 1250 cm^{-1} (ether). In the ^{1}H nmr spectrum the C-7 hydrogen appears at δ 4.42 as a broad singlet. Four methyl singlets are displayed at δ 3.68 (ester), 1.29 (C-1 methyl), 0.89 and 0.82 (*gem*-dimethyl). The ^{13}C nmr APT spectrum gives a carbonyl signal at δ 176.0 (ester) and two signals for the oxygen-bearing carbons at δ 74.8 (C-1) and at 76.6 (C-7). The mass spectrum shows a molecular ion peak at m/z 252.1727, confirming the molecular formula $C_{15}H_{24}O_3$.

The other ester **42** displays the C-8 hydrogen at δ 4.43 (dd, *J* = *J'* = 2 Hz) in its ^1H nmr spectrum. Singlets for the methyl groups are displayed at δ 3.66 (ester), 1.30 (C-1), 0.90 and 0.82 (*gem*-dimethyl). In the ^{13}C nmr APT spectrum, a carbonyl signal appears at δ 176.1. Two signals for the carbons bearing the ether bridge appear at δ 78.5 (C-1) and 76.7 (C-8). The molecular formula $C_{15}H_{24}O_3$ was confirmed by the molecular ion peak at m/z 252.1725 in the high resolution mass spectrum.



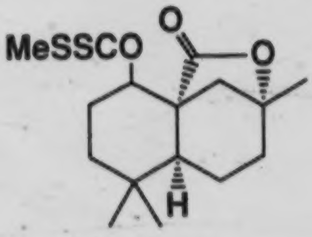
43

Of the four compounds **39** - **42**, **39** and **42** are potentially useful for the current studies. In practice, attempted cleavage of the ether ring present in the minor compound **42** under acidic conditions, failed to give any desired hydroxy lactone **43**. The conversion of trifluoroacetate lactone **39** to lactone **30**, prepared previously via a different route, requires the cleavage of a carbon-oxygen bond. The cleavage of a sterically hindered ester group has been demonstrated by Barton *et al.*[28] by the use of metallic lithium in ethylamine at -78°C. When lactone **39** was subjected to reduction under these conditions for 1 h the only product obtained in 56 % yield was hydroxy lactone **43**.

Pete *et al.*[56] have reported that carboxylic esters are readily reduced to the hydrocarbon level in hexamethylphosphorous triamide (HMPT)-H_2O (95 : 5) upon irradiation with 254 nm UV light. In our case irradiation of **39** with a 12 W low-pressure mercury lamp for 3 h gave again the hydroxy lactone **43** as the only product in approximately 50 % yield.

In a successful indirect procedure, trifluoroacetate **39** was hydrolyzed with 10 % aqueous potassium carbonate in methanol at room temperature to give hydroxy lactone **43** in almost quantitative yield after 24 h. Similar results were obtained by the use of sodium methoxide in methanol at room temperature. As expected, the reaction proceeded more rapidly and the starting material was completely consumed after 10 h. Recrystallization of **43** from ether afforded white crystals which start subliming at 105°C and have a melting point of 120°C.

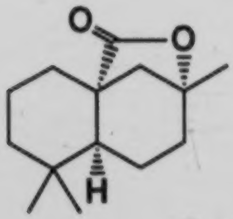
The infrared spectrum of compound **43** shows a broad hydroxy absorption band at 3470 cm^{-1} and a five-membered ring lactone absorption at 1773 cm^{-1}. The ^1H nmr spectrum displays the C-8 proton at δ 3.79 as a doublet of doublets (J = 11, J' = 4 Hz), and the hydroxy proton at δ 2.96 as a broad singlet. The protons attached to the bridge carbon C-12 are displayed as a pair of doublets at δ 2.22 and 1.92 (J = 11 Hz each). Sharp singlets are observed for the methyl groups at δ 1.37 (C-1 methyl), 0.90 and 0.82 (*gem*-dimethyl). In the ^{13}C nmr APT spectrum, a carbonyl signal is displayed at δ 180.1, characteristic of a five-membered ring lactone. The carbons bearing the oxygen atoms are shown at δ 83.2 (C-1) and 70.2 (C-8). High resolution mass spectrometry gave a molecular ion peak at m/z 238.1571, consistent with the molecular formula $C_{14}H_{22}O_3$.



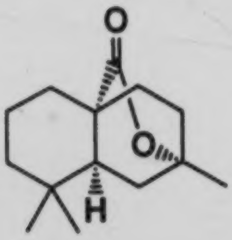
44

Reaction of hydroxy lactone **43** with sodium hydride in 1,2-dimethoxyethane followed by addition of carbon disulfide gave the corresponding sodium xanthate, which was trapped with methyl iodide to form methyl xanthate **44** in 61 % yield. The modest yield is probably due to the steric hindrance of the hydroxy group. The infrared spectrum of compound **44** displays a lactone absorption at 1775 cm^{-1} together with absorption bands at 1224 and 1062 cm^{-1} which confirmed the presence of the xanthate moiety. The ^1H nmr spectrum of shows the C-8 hydrogen signal at δ 5.77 (dd, $J = 9$, $J' = 4$ Hz). The methyl groups are displayed at δ 2.52 (S-CH_3), 1.50 (C-1 methyl), 1.06 and 0.97 (*gem*-dimethyl). The ^{13}C nmr spectrum shows a carbonyl absorption at δ 177.6 an a thiocarbonyl signal at δ 214.5. Signals for the oxygen-bearing carbons are located at δ 82.9 (C-1) and 81.3 (C-8). A molecular ion peak at m/z 328.1169 is displayed in the mass spectrum in agreement with the required molecular formula $C_{16}H_{24}O_3S_2$.

Reduction of the xanthate **44** was carried out under the conditions used previously for the conversion of compounds **22** and **23** to ester **24**. Refluxing a toluene solution of xanthate **44** with tri-*n*-butyltin hydride, in the presence of a catalytic amount of azobisisobutyronitrile, gave a 71 % yield of lactone **30** identical in all respects with the lactone obtained previously by the acid catalyzed cyclization of ester **24**.

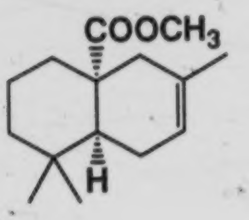


30

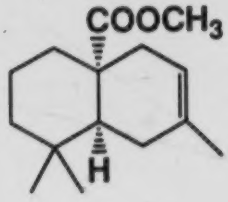


45

Application of the same reaction sequence (**39**→**43**→**44**→**30**) to the mixture of trifluoroacetate lactones **39** and **40** gave isomeric lactones **30** and **45**. The two isomeric lactones were readily separated by flash chromatography on silica gel (0-15 % ether in petroleum ether). Lactone **45** shows a strong carbonyl absorption at 1734 cm^{-1}(lactone). Its ^1H nmr spectrum displays three methyl singlets at δ 1.42 (C-1 methyl), 1.04 and 0.86 (*gem*-dimethyl). The ^{13}C nmr APT spectrum shows a single carbonyl absorption at δ 178.9. The high resolution mass spectrum gives a molecular ion peak at m/z 222.1616 confirming the formula $C_{14}H_{22}O_2$.



24

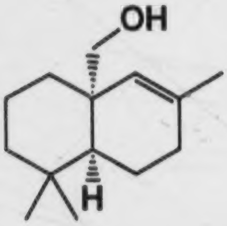


25

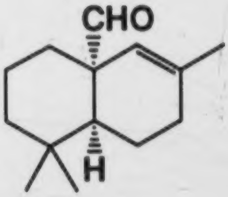
Having recognized that the isomeric lactones **30** and **45** were readily separable, a practical route, which allowed the preparation of compound **30** in large quantity, was developed as follows. An equimolar mixture of isomeric keto esters **13** and **14** was converted to esters **24** and **25** using the route developed earlier for the transformation of pure keto ester **14** to compound **24**, via hydrosilylation, sodium borohydride reduction, xanthate formation and tri-*n*-butyltin hydride reduction. The mixture of **24** and **25** was treated with *p*-toluenesulfonic acid in benzene. Purification by flash chromatography on silica gel (0-15 % ether in petroleum ether) gave lactone **30** (41 % yield) and the isomeric lactone **45** (42 % yield).

By the use of this synthetic sequence a large quantity of **30** was readily obtained in five simple operations with one chromatographic separation. Compound **30** was subsequently reduced to the diol **31** which was converted to alcohol **35** via the hydroxy acetate **32** and olefin **33** according to the procedure described earlier.

The conversion of alcohol **35** to the target molecule **3** requires the modification of the angular substituent. This was achieved in the following manner.



35

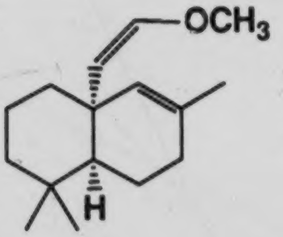


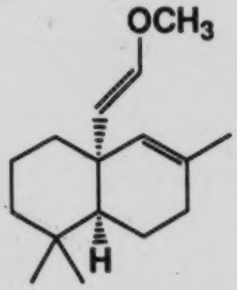
36

Alcohol **35** was oxidized with pyridinium chlorochromate on alumina in dichloromethane. Filtration followed by careful concentration of the filtrate gave the volatile aldehyde **36** in 94 % yield. Two weak bands at 2795 and 2740 cm^{-1} together with a strong carbonyl absorption at 1719 cm^{-1} in the infrared spectrum indicated clearly the presence of an aldehyde group.

In the ${}^1H$ nmr spectrum the aldehyde proton appears at δ 9.27 as a doublet (J = 2 Hz). Three methyl singlets are observed at δ 1.68 (vinylic), 0.95 and 0.86 (*gem*-dimethyl). The ${}^{13}C$ nmr APT spectrum displays a carbonyl signal at δ 204.4. This signal is in antiphase with the signal for deuteriochloroform characteristic of an aldehyde carbonyl. The spectrum also shows two other *sp*^{2} carbons at δ 139.5 and 121.9. High resolution mass spectrometry gave a molecular ion peak at m/z 206.1670 in accordance with the molecular formula $C_{14}H_{22}O$.

Aldehyde **36** underwent a Wittig reaction with (methoxymethyl)triphenylphosphorane in benzene-dimethyl sulfoxide (DMSO). A 1 : 1 mixture of enol ethers **37** and **38** was obtained in 93 % yield. Flash chromatography on silica gel pretreated with 1 % triethylamine in petroleum ether and eluting with the same solvent system, resulted in the separation of these isomers. The use of triethylamine was found to be crucial in order to avoid the hydrolysis of the enol ether functional group during the chromatography.





37 **38**

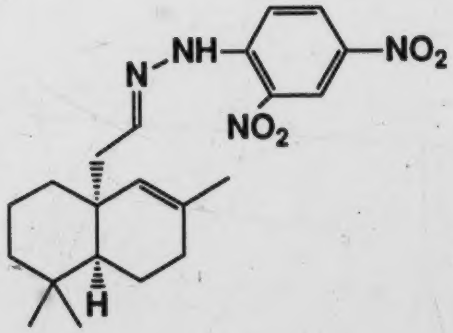
The ^{1}H nmr spectrum of the faster moving isomer displays signals for the vinylic hydrogens of the enol ether moiety at δ 5.64 and 4.27. Each signal appears as a doublet with a small coupling constant of 7 Hz indicating the presence of a *Z* double bond. Accordingly structure **37** was assigned to this compound.

The protons attached to the enol ether double bond are observed at δ 6.11 and 4.71 in the ^{1}H nmr spectrum of the more polar isomer **38**. The *E*-configuration of this double bond is apparent from the large coupling constant of 13 Hz.

To complete the synthesis of isoacanthodoral it remained to hydrolyze the enol ethers **37** and **38**. During the purification of these compounds by flash chromatography on silica gel, it was observed that substantial hydrolysis occurred, apparently due to the acidity of the adsorbent. In fact, it was necessary to use triethylamine in order to circumvent this problem. However, for the conversion of the enol ether moiety to the aldehyde, one would take advantage of the ability of silica gel to induce the hydrolysis for the desired conversion. In order to enhance the acidity of the silica gel, it was washed with glacial acetic acid and then petroleum ether. A flash chromatography of enol ethers **37** and **38** was carried out using this material with ether-petroleum ether elution. Hydrolysis indeed occurred and the desired aldehyde was formed. However a substantial amount of enol ethers **37** and **38** was also recovered. In another experiment, silica gel was prewashed with 70 % perchloric acid and then petroleum ether and flash chromatography was carried out. In this case a greater amount of aldehyde was obtained along with the recovery of a small quantity of enol ethers. However, a substantial loss of material also took place. In a more successful experiment, the mixture of enol ethers was applied to a column containing acetic acid-washed silica gel and the elution with 0-5 % ether-petroleum ether was carried out after 24 h. In this manner, complete hydrolysis occurred and a virtually quantitative yield of the desired aldehyde was obtained. The synthetic isoacanthodoral **3** thus obtained in racemic form shows characteristic aldehyde absorptions at 2845, 2720 and 1720 cm^{-1} in the infrared spectrum. Its ^1H nmr spectrum shows a diagnostic aldehyde signal at δ 9.73 as a doublet of doublets ($J = J' = 3$ Hz) due to the coupling with the adjacent methylenic protons at δ 2.71 (dd, $J = 15$, $J' = 3$ Hz) and 2.13 (dd, $J = 15$, $J' = 3$ Hz). A slightly broad doublet ($J = 1$ Hz) at δ 5.23 could be readily assigned to the vinylic hydrogen. The three methyl singlets are displayed at δ 1.65 (vinylic), 1.00 and 0.91 (*gem*-dimethyl), each as a singlet. A ^{13}C nmr Distortionless Enhanced by Polarization Transfer (DEPT) experiment was employed to determine the multiplicity of each carbon in the molecule. On the basis of this experiment the following assignments were made: δ 204.8 (-**C**=O), 135.5 (-CH=**C**-), 129.9 (-**C**H=C-), 57.2 (-**C**H_2CHO), 46.3 (C-6), 40.1 (-**C**H_2-), 38.5 (-**C**H_2-), 38.2 (C-1), 34.2 (C-7), 32.4 (=C(**C**H_3)), 28.9 (-**C**H_2-), 26.4 (-CH_3), 23.5 (-CH_3), 19.9 (-CH_2-) and 19.2 (-CH_2-). A molecular ion peak at m/z 220.1821 in the high resolution mass spectrum was consistent with the molecular formula $C_{15}H_{24}O$.

A comparison of the ^1H nmr, ^{13}C nmr and mass spectral data of the synthetic material with those reported[4] for the natural isoacanthodoral readily establishes their identicalness.

Naturally occurring isoacanthodoral was isolated in very small quantities only sufficient to obtain spectroscopic data (^1H nmr, ^{13}C nmr and ms).[4] The complete structural assignment was carried out by means of X-ray crystallography on the 2,4-dinitrophenylhydrazone derivative.



8

In order to further confirm the identity of our synthetic (±)-isoacanthodoral it was converted to the 2,4-dinitrophenylhydrazone derivative by treatment with 2,4-dinitrophenylhydrazine (3 % in ethanol-water-H_2SO_4 (2 :2 :1)) at room temperature for 3 h. Flash chromatography of the crude fraction on silica gel (0-5 % ether in petroleum ether), followed by recrystallization from ether-petroleum ether gave orange needles with a melting point of 144-146°C, spectral data is given below

ir ($CHCl_3$ cast): 3302 (NH), 1618 (C=N), 1516 (NO_2) cm^{-1}.

^{1}H nmr (300 MHz, $CDCl_3$): δ 11.02 (N**H**), 9.12 (Ar), 8.29 (Ar), 7.93 (Ar), 7.46 (N=C**H**), 5.14 (C**H**=C), 2.79 (C**H**HC=N), 2.24 (CH**H**C=N), 1.95 (C-4 2 H and C-6), 1.75 (C-5, 1 H), 1.67 (=C(C**H**$_3$)), 1.60-1.10 (C-5, 1 H, C-8, C-9 and C-10), 1.04 (C**H**$_3$) and 0.91 (C**H**$_3$).

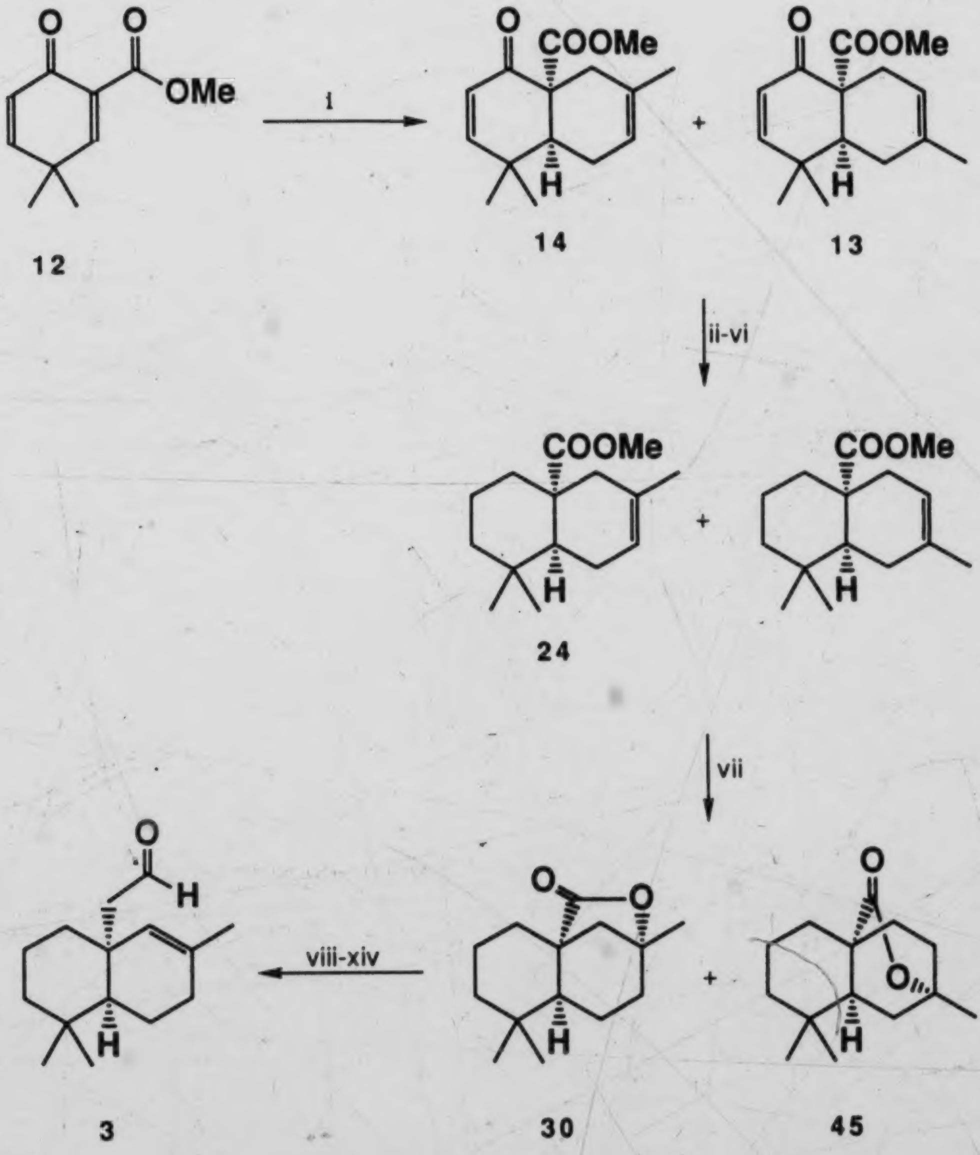
^{13}C nmr APT (75.5 MHz, $CDCl_3$): δ 152.1 (-**C**H=N-), 145.2 (Ar-**C**), 137.8 (Ar-**C**), 135.5 (=**C**(CH_3)), 130.3 (Ar-**C**H), 130.0 (Ar-**C**H), 128.8 (Ar-**C**), 123.6 (Ar-**C**H), 116.6 (-**C**H=C-), 46.5 (-**C**H_2CHN-), 45.8 (-**C**H-), 40.2 (-**C**-), 38.9 (-**C**H_2-), 38.2 (-**C**H_2-), 34.3 (-**C**-), 32.3 (=C(**C**H_3)), 28.9 (-**C**H_2-), 26.5 (-**C**H_3), 23.5 (-**C**H_3), 19.9 (-**C**H_2-) and 19.2 (-**C**H_2-).

mass spectrum: M^+ 400.2116 (calcd. for $C_{21}H_{28}N_4O_4$: 400.2110);

These spectral data were found to be in good agreement with those described for the 2,4-dinitrophenylhydrazone derivative of the natural material.

In conclusion, the marine natural product isoacanthodoral (**3**) has been synthesized in racemic form from 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one in *ca.* 38 % overall yield, using a Diels-Alder approach as outlined in Scheme 3.

Scheme 3


OMe
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i. isoprene, $BF_3 \bullet OEt_2$, ether; ii. Et_3SiH, $(Ph_3P)_3RhCl$; iii. $KHCO_3$, methanol; iv. $NaBH_4$, methanol, -40°C; v. NaH, CS_2, CH_3I, DME; vi. *n*-Bu_3SnH, AIBN, toluene, 110°C, vii. *p*-TsOH, benzene; viii. $LiAlH_4$, ether; ix. Ac_2O, pyridine; x. $POCl_3$, pyridine, DMAP; xi. K_2CO_3, methanol; xii. PCC on Al_2O_3, dichloromethane; xiii. $(C_6H_5)_3P{=}CHOCH_3$, benzene; xiv. aq. AcOH on silica gel.

Experimental

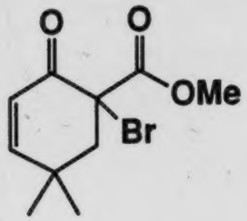
General.

Melting points were measured on a Köfler hot stage apparatus and are uncorrected. Elemental analyses were carried out using a Perkin Elmer 240-B for C, H, N detection. Infrared spectra (ir) were obtained on a Nicolet 7199 FTIR spectrophotometer. Mass spectra (ms) were determined using a AEI Kratos MS-50 high resolution mass spectrometer attached to a Data General Nova 2 with Kratos DS-55 software. Proton nuclear magnetic resonance spectra (^{1}H nmr) were obtained using one of the following spectrometers: Bruker WH-200 (200 MHz), Bruker AM-300 (300 MHz) and Bruker AM-400 (400 MHz). Coupling constants are recorded to within ±0.5 Hz. Carbon-13 nuclear magnetic resonance spectra (^{13}C nmr) were run on a Bruker AM-300 (75 MHz) or a Bruker AM-400 (100.6 MHz). Two methods were used to determine the Carbon-13 multiplicities: the distortionless enhancement by polarization transfer (DEPT) experiment with proton decoupling using a Bruker software microprogram (DEPT.AUR) and the attached proton test (APT) (used for most compounds). Peaks in antiphase (a) with deuteriochloroform were assigned as methyls or methines, while peaks in phase (p) correspond to methylenes or quaternary carbons. Aldehydic carbonyls appear in antiphase with $CDCl_3$ and other carbonyls in phase with the deuteriochloroform signal. Nuclear Overhauser enhancement (nOe) experiments were obtained after computer subtraction of the off-resonance irradiated spectrum from the irradiated spectrum. Positive enhancements are defined as signals in antiphase with the enhanced irradiated signal. Immediately before the experiment each sample was deoxygenated by passing helium gas through the solution for 10 min. Reaction yields are quoted with a degree of purity better than 95% as determined by NMR spectroscopy.

Materials.

Products were purified either by flash chromatography using silica gel 60 (230-400 mesh), distillation using a bulb-to-bulb Kugelrohr apparatus or by fractional crystallization. Reactions were monitored by thin layer chromatography using Merck aluminum-backed plates precoated with silica gel 60 GF_{254}. Solvents were dried and distilled prior to use as follows: ethyl ether and 1,2-dimethoxyethane (DME) from a blue-purple solution of sodium benzophenone ketyl under an argon atmosphere; toluene, benzene, pyridine, dichloromethane and dimethyl sulfoxide (DMSO) from calcium hydride or lithium hydride.

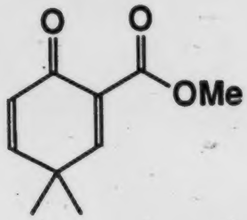
6-Bromo-6-carbomethoxy-4,4-dimethyl-2-cyclohexen-1-one (11).



11

6-Carbomethoxy-4,4-dimethyl-2-cyclohexen-1-one (**10**) (5.12 g, 28.12 mmol) was dissolved in carbon tetrachloride (25 mL) and the reaction vessel was protected from light. *N*-Bromosuccinimide (10.00 g, 56.24 mmol) was added to the solution. After 10 h at room temperature, the suspension was filtered and the residue discarded. The filtrate was concentrated to a residual oil. This was distilled using a Kugelrohr apparatus (100°C, 0.8 torr) to yield a pale yellow oil (6.82 g, 93 %): ^{1}H nmr (200 MHz, $CDCl_3$) δ 6.68 (dd, 1 H, *J* = 2, *J'* = 10 Hz, -C**H**=CHCO), 6.05 (d, 1 H, *J* = 10 Hz, -CH=C**H**CO), 3.82 (s, 3 H, -OC**H**$_3$), 3.03 (dd, 1 H, *J* = 2, *J'* = 14 Hz, -C**H**HCBr), 2.53 (d, *J* = 14 Hz, -CH**H**CBr), 1.28 (s, 3 H, -C**H**$_3$) and 1.13 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75 MHz, $CDCl_3$) δ 187.7 (p), 169.0 (p), 158.5 (a), 124.1 (a), 61.9 (p), 53.7 (a), 48.8 (p), 35.2 (p), 30.1 (a) and 27.6 (a); ir ($CHCl_3$ cast) 1734 (ester) and 1698 cm^{-1} (α,β-unsaturated ketone); ms M$^+$ 260.0048 (calcd. for $C_{10}H_{13}O_3Br$: 260.0049).

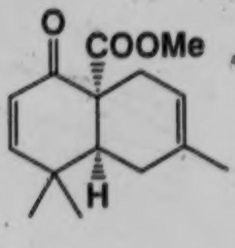
2-Carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (12).



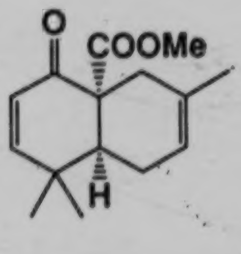
12

Bromide **11** (6.8 g, 26.0 mmol) was dissolved in benzene (30 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.8 mL, 39 mmol) was added dropwise at room temperature to the magnetically stirred solution. After 2 h the solid, which had precipitated from the reaction mixture, was removed by filtration using a sintered glass funnel packed with Florisil as filter-aid. The filtrate was extracted with ethyl ether (3 x 20 mL). The combined organic extracts, were washed successively with 5 % HCl solution (2 x 20 mL), water (1 x 20 mL), saturated sodium bicarbonate solution (1 x 20 mL) and brine (1 x 20 mL). The organic solution was then dried ($MgSO_4$), filtered, and concentrated. Bulb-to-bulb distillation (100°C/0.5 torr) of the concentrate gave a colorless oil (3.7 g, 78 %) which was identical in all respects to the cyclohexadienone prepared using SeO_2 in acetic acid.[64]

(1R*, 6S*)-1-Carbomethoxy-5,5,8-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (13) and (1R*, 6S*)-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (14).



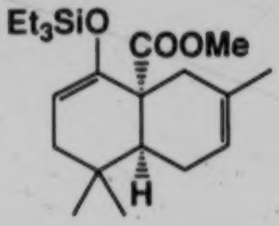
13



14

2-Carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**12**) (8.75 g, 48.6 mmol) was dissolved in dry ether (350 mL) and the solution cooled with an ice-water bath. Isoprene (97 mL, 972 mmol, 20 eq) was added all at once, then boron trifluoride etherate (3 mL, 11.7 mmol, 0.24 eq) was slowly introduced into the reaction flask by means of a syringe. The reaction mixture was stirred at room temperature for 96 h. The reaction was quenched by careful addition of saturated sodium bicarbonate (75 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 50 mL). The organic extracts were combined, washed with water (2 x 20 mL) and brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated to afford a colorless oil. Purification by flash column chromatography on silica gel (0-10 % ether in petroleum ether) gave a mixture of Diels-Alder adducts (11.6 g, 46.7 mmol, 96 %) **13** and **14** in a 3:7 ratio. The major isomer was isolated by fractional crystallization by seeding the ether solution of the mixture of the adducts with pure crystals of compound **14**, which were obtained by preparative high pressure liquid chromatography of the mixture using a Waters Associates Prep LC/System 500 instrument charged with a silica gel cartridge, using a solution of 5 % ethyl acetate in *n*-hexane as eluent. Repeated crystallization with seeding (x 3) yielded 4.0 g (16.1 mmol, 34.5 %) of compound **14** as white crystals: m.p. 97-98°C; ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.54 (d, 1 H, J = 10 Hz, -C**H**=CHCO), 5.86 (d, 1 H, J = 10 Hz, -CH=C**H**CO), 5.32 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 3.72 (s, 3 H, $-COOC\mathbf{H}_3$), 2.66 (ddd, 1 H, J = 6, J' = 4, J'' = 1, $-C(CH_3)_2C\mathbf{H}CH_2-$), 2.49 (d, 1 H, J = 17 Hz, $-C\mathbf{H}HC(CH_3)=$), 2.12 (d, 1 H, J = 17 Hz, $-CH\mathbf{H}C(CH_3)=$), 2.10-2.00 (complex, 2 H, $-C\mathbf{H}\mathbf{H}CH=C(CH_3)-$), 1.64 (s, 3 H, $-C(C\mathbf{H}_3)=CH-$), 1.14 (s, 3 H, $-C(C\mathbf{H}_3)_2$) and 0.99 (s, 3 H, $-C(C\mathbf{H}_3)_2$); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 197.3 (p), 173.1 (p), 157.8 (a), 131.3 (p), 124.1 (a), 119.3 (a), 57.6 (p), 52.4 (a), 40.6 (a), 36.1 (p), 33.3 (p), 30.5 (a), 24.4 (p), 23.8 (a), and 23.1 (a); ir ($CHCl_3$ cast) 1739 (ester) and 1667 cm^{-1} (α,β-unsaturated ketone); ms M^+ 248.1418 (calcd. for $C_{15}H_{20}O_3$: 248.1412). Anal. calcd. for $C_{15}H_{20}O_3$: C, 72.54; H, 8.12; found: C, 72.36; H, 8.04. The minor isomer was not obtained in pure form.

(1R*, 6S*)-1-Carbomethoxy-5,5,9-trimethyl-2-triethylsiloxybicyclo[4.4.0]deca-2,8-diene (15)

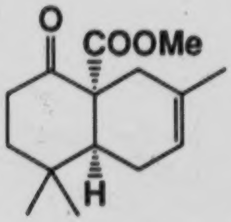


15

A dichloromethane solution of keto ester **14** (3.50 g, 14.00 mmol) was allowed to evaporate to dryness slowly in order to produce very fine crystals. These were suspended in triethylsilane (4.50 mL, 28.00 mmol), and tris(triphenylphosphine)rhodium(I) chloride (64 mg, 0.07 mmol) was added. The slurry was stirred for 5 h at room temperature, then additional triethylsilane (4.50 mL, 28.00 mmol) was added. The reaction was stirred overnight (approx. 12 h), after which time all the solid keto ester dissolved. The reaction mixture was diluted with petroleum ether, filtered through Florisil contained in a sintered glass funnel, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (0-10% ether in petroleum ether) gave silyl enol ether **15** as a colorless oil (4.95 g, 97 %): ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.35 (br s, 1 H, -C=C**H**-), 4.67 (dd, 1 H, *J* = 2, *J'* = 6 Hz, -SiO-C=C**H**-), 3.65 (s, 3 H, -COOC**H$_3$**), 2.66 (d, 1 H, *J* = 17 Hz, -SiOC=CHC**H**H-), 2.25-1.90 (complex, 5 H), 1.79 (dd, 1 H, *J* = 6.0, *J'* = 17 Hz, -SiOC=CHCH**H**-), 1.67 (br s, 3 H, =CC**H$_3$**), 0.97

(complex, 15 H, -C(C**H**$_3$)$_2$ and -Si(CH$_2$C**H**$_3$)$_3$) and 0.66 (q, 6 H, -Si(C**H**$_2$CH$_3$)$_3$); ^{13}C nmr APT (100.6 MHz, CDCl$_3$) δ 176.3 (p), 151.0 (p), 131.9 (p), 118.8 (a), 99.1 (a), 51.9 (a), 51.5 (p), 42.1 (a), 39.7 (p), 35.1 (p), 32.3 (p), 31.0 (a), 23.5 (p), 23.3 (a), 22.6 (a), 6.7 (a), and 5.1 (p); ir (CHCl$_3$ cast) 1742, 1729 (ester) and 1670 cm^{-1} (olefin); ms M$^+$ 364.2440 (calc. for $C_{21}H_{36}O_3Si$: 364.2434).

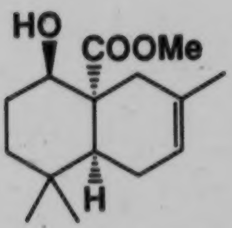
(1R*, 6S*)-1-Carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]deca-8-en-2-one (16)



16

Silyl enol ether **15** (1.00 g, 2.75 mmol) was dissolved in methanol and a 10% aqueous solution of potassium bicarbonate (50 mL) was added. The mixture was stirred at room temperature for 10 h, then poured into water. The water layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed successively with water (2 x 10 mL) and brine solution (1 x 10 mL), then dried (MgSO$_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (0-5 % ethyl acetate in petroleum ether) gave a quantitative yield of keto ester **16** (0.69 g) as white crystals: m.p. 41-42°C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.32 (br s, 1 H, -C=C**H**-), 3.70 (s, 3 H, -COOC**H**$_3$), 2.60-2.45 (m, 3 H,), 2.37 (br s, 2 H, 2.10 (complex d, 1 H, J = 18 Hz, -C**H**HCH=C(CH$_3$)-), 1.90 (complex d, 1 H, J = 18, -CH**H**CH=C(CH$_3$)-), 1.82 (dd, 1 H, J = 7, J' = 6 Hz), 1.72 (dd, 1 H, J = 9, J' = 6 Hz), 1.68 (s, 3 H, -C(C**H**$_3$)=CH-), 1.10 (s, 3 H, -C**H**$_3$) and 1.02 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 207.3 (p), 172.9 (p), 129.8 (p), 118.4 (a), 59.6 (p), 51.6 (a), 43.4 (a), 37.5 (p), 34.9 (p), 33.0 (p), 32.6 (p), 29.8 (a), 23.6 (p), 23.5 (a) and 22.4 (p); ir (neat) 1743, 1731 (ester) and 1711 cm^{-1} (ketone); ms M$^+$ 250.1578 (calcd. for $C_{15}H_{22}O_3$: 250.1569). Anal. calcd. for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86; found: C, 71.64; H, 8.78.

(1R*, 2R*, 6S*)-1-Carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (19), (1R*, 2S*, 6S*)-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (20) and (1R*, 6S*)-1-hydroxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (21)



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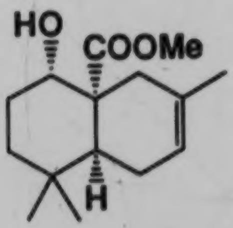
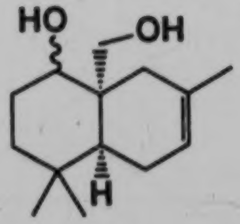


20

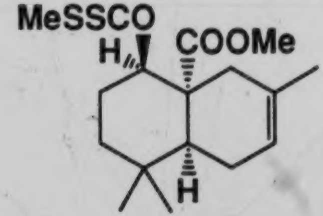


21

Sodium borohydride (0.46 g, 12.2 mmol, 1.7 eq) was slowly added during 30 min to a stirred, cooled (-40°C) solution of keto ester **16** (1.80g, 7.2 mmol) in methanol (15 mL). The reaction mixture was left to react for 15 min, quenched with a saturated aqueous solution of ammonium chloride (1 mL) at -40°C, then allowed to warm to room temperature. The reaction mixture was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (2 x 5mL) and brine(1 x 5mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the concentrate by flash chromatography on silica gel (0-30% ethyl acetate in petroleum ether) led to the isolation of two epimeric alcohols **19** and **20** (1.7 g, 95 %) in a ratio of 5 : 1. The major alcohol (**19**) was obtained as a colorless oil: ^1H nmr (400 MHz, $CDCl_3$) δ 5.27 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 3.90 (ddd, 1 H, $J = 9$, $J' = 7$, $J'' = 4$ Hz, $-C\mathbf{H}OH$), 3.72 (s, 3 H, $-OC\mathbf{H}_3$), 2.45 (d, 1 H, $J = 16$ Hz, $-C\mathbf{H}HC(CH_3)=$), 2.12 (d, 1 H, $J = 16$ Hz, $-CH\mathbf{H}C(CH_3)=$), 2.05 (m, 2 H, $-C\mathbf{H}_2CH=$), 1.93 (dd, 1 H, $J = 7$, $J' = 1.5$ Hz, $-C(CH_3)_2C\mathbf{H}CH_2-$), 1.88 (d, 1 H, $J = 4$ Hz, $-O\mathbf{H}$), 1.73 (dd, 1 H, $J = 4$, $J' = 2$ Hz, $-C\mathbf{H}HCHOH$), 1.70 (dd, 1 H, $J = 7$, $J' = 4$ Hz, $-CH\mathbf{H}CHOH$), 1.68 (s, 3 H, $-C(C\mathbf{H}_3)=CH-$), 1.47 (ddd, 1 H, $J = 13.5$, $J' = = 3.5$, $J'' = 3.5$ Hz, $-C\mathbf{H}HC(CH_3)_2-$), 1.40 (ddd, 1 H, $J = 13.5$, $J' = 10$, $J'' = 7$ Hz, $-CH\mathbf{H}C(CH_3)_2-$), 0.94, (s, 3 H, $-C\mathbf{H}_3$) and 0.83 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 177.6 (p), 131.8 (p), 119.7 (a), 75.4 (a), 52.4 (p), 52.2 (a), 41.9 (a), 39.3 (p), 33.1 (p), 32.8 (a), 28.5 (p), 27.2 (p), 24.4 (p), 23.5 (a) and 21.7 (a); ir ($CHCl_3$ cast) 3470 (alcohol) and 1737 cm^{-1} (ester); ms M^+ 252.1729 (calcd. for $C_{15}H_{24}O_3$:

252.1726). The minor alcohol **20** was obtained as white needles: m.p. 42-44°C; ^{1}H nmr (400 MHz, CDCl$_3$) δ 5.35 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 3.70 (s, 3 H, $-OC\mathbf{H}_3$), 3.60 (ddd, 1 H, *J* = 10, *J'* = 7, *J''* = 7 Hz, $-C\mathbf{H}OH$), 3.06 (br s, 1 H, $-O\mathbf{H}$), 2.49 (d, 1 H, *J* = 17 Hz, $-C\mathbf{H}HC(CH_3)=CH-$), 2.30-2.15 (complex, 3 H, $-CH\mathbf{H}C(CH_3)=CH-$, $-C(CH_3)_2C\mathbf{H}CH_2-$ and $-CH\mathbf{H}CH=C(CH_3)-$), 2.00 (m, 1 H, $-C\mathbf{H}HCH=$), 1.87 (dd, 2 H, *J* = 13, *J'* = 7 Hz, $-C\mathbf{H}_2CHOH$), 1.66 (br s, 3 H, $-C(C\mathbf{H}_3)=CH-$), 1.54 (ddd, 1 H, *J* = 14, *J'* = 14, *J''* = 7 Hz, $-CH\mathbf{H}C(CH_3)_2-$), 1.40 (ddd, 1 H, *J* = 14, *J'* = 5.5, *J''* = 5 Hz, $-C\mathbf{H}HC(CH_3)_2-$), 0.96 (s, 3 H, $-C\mathbf{H}_3$) and 0.89 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr APT (75.5 MHz, CDCl$_3$) δ 178.8 (p), 129.6 (p), 119.8 (a), 69.7 (a), 51.4 (a), 49.7 (p), 40.4 (a), 35.3 (p), 33.7 (p), 33.5 (p), 29.5 (a), 27.8 (p), 24.7 (p), and 23.1 (a); ir (CHCl$_3$ cast) 3529 (alcohol) and 1739 cm^{-1} (ester). Further elution gave diol **21** in 3-5 % yield. Recrystallization from acetone gave white needles which started subliming at 150°C: ^{1}H nmr (400 MHz, CD$_3$OD) δ 5.22 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 4.51 (br s, 1 H, $-O\mathbf{H}$), 3.65 (dd, 1 H, *J* = 12, *J'* = 4 Hz, $-C\mathbf{H}OH$), 3.53 (d, 1 H, *J* = 10 Hz, $-C\mathbf{H}HOH$), 3.26 (d, 1 H, *J* = 10 Hz, $-CH\mathbf{H}OH$), 3.22 (br d, 1 H, *J* = 1 Hz, $-O\mathbf{H}$), 2.00-1.30 (complex m, 9 H), 1.54 (s, 3 H, $-C(C\mathbf{H}_3)=CH-$), 0.82 (s, 3 H, $-C\mathbf{H}_3$) and 0.75 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr (100.6 MHz, CD$_3$OD) δ 132.5, 121.2, 121.0, 74.7, 67.4, 43.1, 40.9, 34.5, 33.4, 30.5, 27.7, 24.2, 24.0 and 22.4; ir (Nujol) 3290 cm^{-1} (alcohol); ms M$^+$ 224.1774 (calcd. for $C_{14}H_{24}O_2$: 224.1777).

(1R*, 6S*, 10R*)-1-Carbomethoxy-3,7,7-trimethyl-10-(methylmercaptothiocarbonyloxy)bicyclo[4.4.0]dec-3-ene (22) and (1R*, 6S*, 10S*)-1-carbomethoxy-3,7,7-trimethyl-10-(methylmercaptothiocarbonyloxy)bicyclo[4.4.0]dec-3-ene (23)



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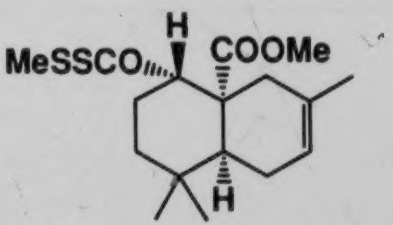
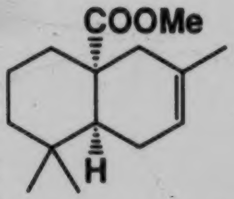


23

Sodium hydride (80 % dispersion in mineral oil, 0.95 g, 32 mmol) was slowly added to a cooled (0°C) solution of hydroxyester **20** or **21** (or the mixture of both) (2.00 g, 7.94 mmol) in 1,2-dimethoxyethane (34 mL). After 20 min carbon disulfide (1.8 mL, 29.8 mmol, 3.75 eq) was introduced to the reaction vessel, followed by methyl iodide (6.2 mL, 100 mmol, 12.5 eq). The reaction mixture was then allowed to warm up to room temperature. After 10 h of stirring the solution was poured into ice-water. The aqueous layer was extracted with ether (3 x 15 mL). The combined ether extracts were washed with water (1 x 15 mL) and brine (1 x 15 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the concentrate by flash chromatography on silica gel (0 to 10% ether in petroleum ether) gave a quantitative yield of the xanthate **22** or **23** (or the epimeric mixture) (2.70 g, 7.89 mmol). Compound **22** was isolated as a yellow oil: ^1H nmr (400 MHz, $CDCl_3$) δ 5.96 (dd, 1 H, J = 11.5, J' = 4.5 Hz, $-C\mathbf{H}OCSSCH_3$), 5.26 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 3.62 (s, 3 H, $-OC\mathbf{H}_3$), 2.54 (d, 1 H, J = 18 Hz, $-CH\mathbf{H}C(CH_3)=CH-$), 2.52 (s, 3 H, $-SCH_3$), 2.28 (d, 1 H, J = 18 Hz, $-C\mathbf{H}HC(CH_3)=CH-$), 1.98-2.06 (complex, 4 H, $-C(CH_3)_2C\mathbf{H}CH_2-$, $-CHC\mathbf{H}_2CH=$, and $-C\mathbf{H}HCHO$), 1.79 (dddd, 1 H, J = 12, J' = 12, J'' = 8.5, J''' = 8.5 Hz, $-CH\mathbf{H}CHO$), 1.69 (s, 3 H, $-C(C\mathbf{H}_3)=CH-$), 1.52 (dd, 2 H, J = 8.5, J' = 3.5 Hz, $-C\mathbf{H}_2C(CH_3)_2CH-$), 0.96 (s, 3 H, $-C\mathbf{H}_3$) and 0.87 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 214.9 (p), 175.5 (p), 131.9 (p), 119.3 (a), 86.8 (a), 52.5 (a), 51.1 (p), 42.6 (a), 38.9 (p), 33.1 (p), 32.6 (a), 29.8 (p), 24.1 (p), 23.6 (a), 23.4 (p), 21.9 (a) and 18.8 (a); ir ($CHCl_3$ cast) 1737 (ester) and 1240 cm^{-1} (xanthate); ms M^+ 342.1315 (calcd. for $C_{17}H_{26}O_3S_2$: 342.1338). Compound **23** was isolated as a red oil: ^1H nmr (400 MHz, $CDCl_3$) δ 5.74 (dd, 1 H, $J = J'$ = 3 Hz, $-C\mathbf{H}OCSSCH_3$), 5.28 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 3.55 (s, 3 H, $-OCH_3$), 2.55-2.45 (m, 1 H, $-C\mathbf{H}HCHO-$), 2.50 (s, 3 H, $-SCH_3$), 2.34 (d, 1 H, J = 18 Hz, $-C\mathbf{H}HC(CH_3)=$), 2.26 (d, 1 H, J = 8 Hz, $-CH\mathbf{H}CHO-$), 2.13 (d, 1 H, J = 18 Hz, $-CH\mathbf{H}C(CH_3)=$), 2.06 (br s, 1 H, $-C(CH_3)_2C\mathbf{H}CH_2-$), 2.00 (ddd, 1 H, J = 15, J' = 7, J'' = 4 Hz, $-CHC\mathbf{H}HCH=$), 1.88 (ddd, 1 H, J = 14, J' = 4, J'' = 2 Hz, $-CHCH\mathbf{H}CH=$), 1.54 (s, 3 H, $-CH2C(C\mathbf{H}_3)=CH-$), 1.46 (ddd, 1 H, J = 14, J' = 13, J'' = 4 Hz, $-C\mathbf{H}HC(CH_3)_2-$), 1.23 (ddd,1 H, J = 14, J' = 4, J'' = 4 Hz, $-CH\mathbf{H}C(CH_3)_2-$), 0.96 (s, 3 H, $-C\mathbf{H}_3$) and 0.81 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 213.9 (p), 174.6 (p), 129.3 (p), 121.7 (a), 84.1 (a), 52.0 (a), 50.2 (p), 37.8 (a), 34.9 (p), 34.0 (p), 33.3 (p), 32.9 (a), 24.3 (p), 23.5 (a), 22.2 (p), 21.5 (a) and 18.4 (a); ir ($CHCl_3$ cast) 1738 (ester) and 1232 cm^{-1} (xanthate).

(1R*, 6S*)-1-Carbomethoxy-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene (24)

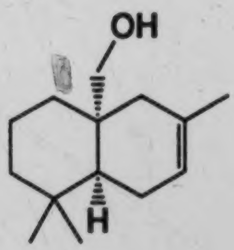


24

Argon was bubbled for 30 min through a solution of xanthate **22** or **23** (or the mixture) (2.6 g, 7.70 mmol) in dry toluene (100 mL), then tri-*n*-butyltin hydride (3.10 mL, 11.5 mmol, 1.5 eq) was added followed by a catalytic amount of azobisisobutyronitrile (AIBN, 54 mg, 0.33 mmol, 0.04 eq). The solution was refluxed for 10 h, cooled down and concentrated under reduced pressure. Purification of the residual oil by flash chromatography on silica gel (0 to 5% ether in petroleum ether) gave ester **24** (1.73 g, 7.32 mmol, 95 % yield) as a colorless oil: ^1H nmr (400 MHz, $CDCl_3$) δ 5.30 (br s, 1 H, -C(CH_3)=C**H**-), 3.68 (s, 3 H, -OC**H**$_3$), 2.32 (d, 1 H, *J* = 18 Hz), 2.20-2.00 (m, 3 H), 1.64 (s, 3 H, -CH_2C(C**H**$_3$)=), 1.60-1.50 (complex, 4 H), 1.45 (m, 1 H), 1.36 (dddd, 1 H, *J* = 15, *J'* = 15, *J''* = 7, *J'''* = 2 Hz), 1.24 (m, 1 H), 0.96 (s, 3 H, -C**H**$_3$) and 0.88 (s, 3 H, -C**H**$_3$); ^{13}C nmr

APT (100.6 MHz, $CDCl_3$) δ 178.8 (p), 131.2 (p), 119.8 (a), 51.6 (a), 46.2 (p), 41.3 (a), 39.2 (p), 36.4 (p), 33.5 (p), 31.7 (a), 24.7 (p), 24.1 (a), 23.3 (a) and 18.9 (p); ir (neat) 1730 cm^{-1} (ester); ms M^+ 236.1780 (calcd. for $C_{15}H_{24}O_2$: 236.1776).

(1R*, 6S*)-1-Hydroxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene (26)

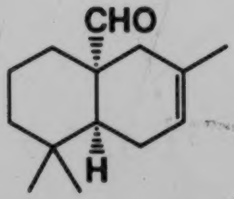


26

Lithium aluminum hydride (0.20 g, 5.27 mmol) was slowly added to a cooled (ice-water), dry ether solution (8 mL) of ester **24** (0.24 g, 1.03 mmol). The solution was stirred for 3 h at room temperature before it was poured into a saturated aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 5 mL) and brine (2 x 5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the concentrate by flash column chromatography (0-15% ether in petroleum ether) gave alcohol **26** (0.21 g, 96 %) as a crystalline solid: m.p. 67-68°C; ^1H nmr (400 MHz, $CDCl_3$) δ 5.29 (ddd, 1 H, J = 7, J' = 3,

J'' = 1.5 Hz, -C(CH_3)=C**H**-), 3.39 (d, 1 H, J = 10 Hz, -C**H**HOH), 3.27 (d, 1 H, J = 10 Hz, -CH**H**OH), 2.16-2.00 (complex, 3 H), 1.62 (s, 3 H, -C(C**H**$_3$)=CH-), 1.50-1.10 (complex, 9 H), 0.94 (s, 3 H, -C**H**$_3$) and 0.84 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 131.6 (p), 119.7 (a), 71.4 (p), 42.4 (p), 41.2 (a), 37.4 (p), 34.4 (p), 34.3 (p), 33.7 (p), 33.3 (a), 23.6 (a), 23.5 (p), 21.8 (a) and 18.3 (p); ir ($CHCl_3$ cast) 3280 cm^{-1} (alcohol); ms M^+ 208.1833 (calcd. for $C_{14}H_{24}O$: 208.1827). Anal. calcd. for $C_{14}H_{24}O$: C, 80.70; H, 11.62; found: C, 80.87; H, 11.65.

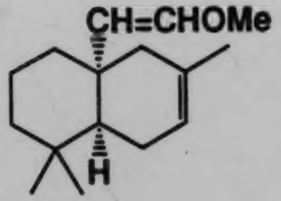
(1R*, 6S*)-1-Formyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene (27)



27

Pyridinium chlorochromate impregnated on alumina (1.19 g, 0.93 mmol/g, 2.3 eq) was added to a solution of alcohol **26** (114 mg, 0.55 mmol) in dry dichloromethane (7 mL). The reaction was magnetically stirred at room temperature for 2 h, before it was filtered through a sintered-glass filter filled with Florisil. The reaction mixture was washed with dichloromethane (10 mL). Concentration of the dichloromethane solution using a rotary-evaporator under slightly reduced pressure (the compound is rather volatile), afforded a colorless oil which was pure as demonstrated by nmr analysis (99 mg, 0.48 mmol, 88 %): ^{1}H nmr (400 MHz, $CDCl_3$) δ 9.32 (s, 1 H, -C**H**O), 5.32 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 2.10-1.90 (complex, 4H), 1.67 (s, 3 H, $-C(C\mathbf{H}_3)=CH-$), 1.70-1.44 (complex, 5 H), 1.35 (m, 1 H), 1.24 (m, 1 H), 0.96 (s, 3 H, $-C\mathbf{H}_3$) and 0.86 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 205.6 (a), 130.7 (p), 120.5 (a), 49.1 (p), 40.6 (a), 39.4 (p), 33.3 (p), 31.7 (a), 29.8 (p), 24.2 (a), 23.9 (a), 23.5 (p) and 18.2 (p); ir (neat) 2840, 2700 and 1724 cm^{-1} (aldehyde); ms M$^+$ 206.1673 (calcd. for $C_{14}H_{22}O$: 206.1670). Anal. calcd. for $C_{14}H_{22}O$: C, 81.48; H, 10.75; found: C, 81.62; H, 10.70.

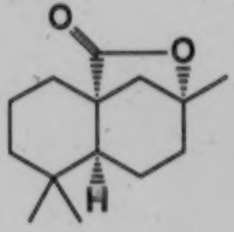
(1R*, 6S*)-1-(2-Methoxyethenyl)-3,7,7-trimethylbicyclo[4.4.0]-dec-3-ene (28)



28

Potassium hydride (35 % oil dispersion, 0.105 g, 1.04 mmol) was washed with dry ether (3 x 1 mL), and the washings were discarded. The dry potassium hydride was covered with dry benzene (1 mL), then dry dimethyl sulfoxide (0.55 mL) was added at room temperature. After all of the solid had dissolved, a solution of (methoxymethyl)triphenylphosphonium chloride (374 mg, 1.09 mmol) in benzene (0.5 mL) was added and the resulting mixture allowed to react until a deep red-burgandy color solution developed (about 30 min). Aldehyde **27** (41 mg, 0.2 mmol) in benzene (0.5 mL) was added slowly and the reaction mixture was stirred for 10 h. The reaction mixture was poured into ice-water and the aqueous layer extracted with ether (4 x 2 mL). The organic extracts were combined, washed with water (1 x 2 mL) and brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated to yield a colorless oil. Purification of the oil by bulb-to- bulb distillation gave 45.5 mg (98 %) of a 1 : 1 mixture of enol ethers **28**, which were not separated: ^1H nmr (400 MHz, $CDCl_3$) δ 6.18; 5.63 (d, 1 H, J = 13 Hz; d, 1 H, J = 7.5 Hz, $-CH{=}C\mathbf{H}OCH_3$), 5.32 (br s, 2 H, $-C(CH_3){=}C\mathbf{H}-$), 4.77; 4.17 (d, 1 H, J = 13 Hz; d, 1 H, J = 7.5 Hz, $-C\mathbf{H}{=}CHOCH_3$), 3.52; 3.48 (both s, 3 H each, $-CH{=}CHOC\mathbf{H}_3$), 2.32-2.12 (complex, 4 H), 2.05 (br d, 2 H, J = 18 Hz), 1.85 (br d, 1 H, J = 16.5 Hz), 1.61 (br s, 6 H, $-C(C\mathbf{H}_3){=}CH-$), 1.70-1.05 (complex, 15 H), 0.92; 0.90; 0.83 and 0.81 (s, 3 H each, 4 x $-C\mathbf{H}_3$); ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 145.1, 144.6, 132.4, 131.3, 120.7, 120.2, 118.6, 116.0, 59.6, 55.9, 47.0, 44.7, 42.2, 41.6, 39.2, 38.1, 37.8, 36.9, 36.6, 36.2, 34.0, 33.9, 33.6, 24.4, 24.2, 23.9, 23.6, 22.5, 22.3, 19.2, and 18.8; ir (neat) 1651 (olefin) and 1205 cm^{-1} (ether); ms M^+ 234.1984 (calcd. for $C_{16}H_{26}O$: 234.1984).

(1R*, 4S*, 9R*)-1,5,5-Trimethyl-11-oxa-tricyclo[7.2.1.0^{4,9}]-dodecan-10-one (30).



30

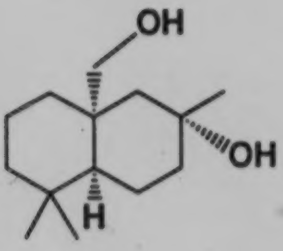
p-Toluenesulfonic acid monohydrate (PTSA•H_2O) (450 mg, 2.40 mmol) was added to a solution of ester **24** (0.23 g, 0.96 mmol) in benzene (5 mL). The reaction mixture was refluxed for 3 h with removal of water by means of a Dean-Stark trap. The solution was cooled, washed successively with saturated sodium bicarbonate solution (1 x 3 mL), water (2 x 3 mL) and brine (1 x 3 mL), dried ($MgSO_4$), filtered and concentrated. Purification by recrystallization from petroleum ether or by flash chromatography (0-3 % ether in petroleum ether) gave lactone **30** (177 mg, 0.80 mmol, 90 %) as white needles: m.p. 87-88°C; ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.38 (d, 1 H, J = 12 Hz, -CC**H**HC(CH_3)O-), 1.90-1.70 (complex, 4 H), 1.62 (m, 2 H), 1.60-1.46 (complex, 3 H), 1.45 (s, 3 H, -CH_2C(C**H**$_3$)O-), 1.40-1.20 (complex, 3 H), 1.01 (s, 3 H, -C**H**$_3$) and 0.95 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 181.0 (p), 82.8 (p), 49.5 (p), 43.6 (p), 42.8 (a), 40.8 (p), 34.6 (p), 33.2 (p), 33.1 (a), 32.8 (p), 25.3 (a), 22.7 (a), 19.5 (p) and 19.2 (p); ir (CH_2Cl_2 cast)

1753 cm^{-1} (lactone); ms M$^+$ 222.1619 (calcd. for $C_{14}H_{22}O_2$: 222.1619). Anal. calcd. for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98; found: C, 75.64; H, 9.95.

Lactone 30 from xanthate 44.

Tri-*n*-butyltin hydride (75 mg, 0.25 mmol) and a catalytic amount of azoisobutyronitrile (~10 mg), were added to a solution of xanthate **44** (56 mg, 0.17 mmol) in toluene. Argon was bubbled through the solution for 20 min, then the reaction mixture was refluxed for 10 h. Concentration of the solution *in vacuo* and purification of the product by flash chromatography on silica gel (0-15 % ether in petroleum ether) gave lactone **30** (27 mg, 0.12 mmol, 71 %).

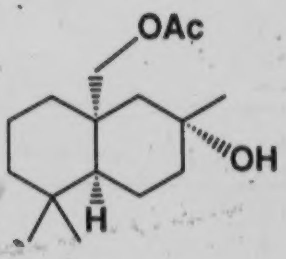
(1R*, 3R*, 6S*)-1-Hydroxymethyl-3,7,7-trimethylbicyclo[4.4.0]-decan-3-ol (31)



31

A solution of lactone **30** (1.84 g, 8.30 mmol) in dry ether (60 mL) was cooled in an ice-water bath. After 10 min, lithium aluminum hydride (1.55 g, 40.8 mmol) was carefully added and the resulting mixture allowed to warm to room temperature. After 1 h the reaction mixture was cooled with an ice-water bath. After one additional hour, water (10 mL) was slowly added followed by 10 % sodium hydroxide (10 mL) and then water again (10 mL). The water layer was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, washed with water (2 x 5 mL) and brine (1 x 5 mL), dried ($MgSO_4$), filtered, and concentrated. Crystallization of the concentrate from petroleum ether gave a crystalline solid (1.82 g, 8.05 mmol, 97 %): m.p. 104-105°C; ^1H nmr (300 MHz, $CDCl_3$) δ 3.98 (d, 1 H, *J* = 11 Hz, -C**H**HOH), 3.14 (d, 1 H, *J* = 11 Hz, -CH**H**OH), 1.97 (m, 2 H, -**CH**$_2$C(CH_3)OH), 1.80-1.30 (complex, 10 H), 1.23 (s, 3 H, -C(**CH**$_3$)OH), 1.20-1.10 (br d, 1 H, *J* = 6 Hz), 0.98 (s, 3 H, -CH_3) and 0.95 (s, 3 H, -**CH**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 74.1 (p), 70.6 (p), 43.0 (p), 42.6 (a), 40.5 (p), 38.7 (p), 37.9 (p), 36.2 (p), 34.3 (p), 33.4 (a), 33.2 (a), 26.8 (a), 19.3 (p) and 18.2 (p); ir ($CHCl_3$ cast) 3349 cm^{-1} (alcohol); ms M^+ 226.1924 (calcd. for $C_{14}H_{26}O_2$: 226.1933). Anal. calcd. for $C_{14}H_{26}O_2$: C, 74.27; H, 11.58; found: C, 73.87; H, 11.43.

(1R*, 3R*, 6S*)-1-Acetoxymethyl-3,7,7-trimethylbicyclo[4.4.0]-decan-3-ol (32)

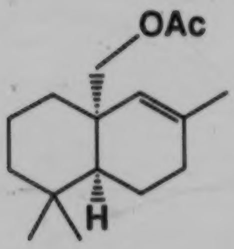


32

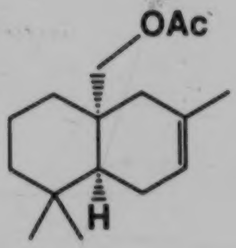
Diol **31** (1.80 g, 8.05 mmol) was dissolved in dry pyridine (10 mL) at room temperature. Acetic anhydride (7.60 mL, 80.5 mmol) was added and the reaction mixture stirred overnight (10 h). Methanol (4.0 mL, 100 mmol) was added and the resulting mixture was stirred for an additional 3 h before water (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). The organic extracts were combined and washed successively with 5 % HCl solution (2 x 10 mL), water (2 x 10 mL) and brine (1 x 5 mL), dried ($MgSO_4$), filtered and concentrated. The oily residue was purified by flash chromatography (0 to 10 % ethyl acetate in petroleum ether) to afford hydroxy acetate **32** as a colorless oil (1.95 g, 7.26 mmol, 90 %): ^{1}H nmr (300 MHz, $CDCl_3$) δ 4.31 (d, 1 H, *J* = 11 Hz, -C**H**HOAc), 4.14 (d, 1 H, *J* = 11 Hz, -CH**H**OAc), 2.07 (s, 3 H, -COC**H**$_3$), 2.00-1.80 (m, 1 H), 1.73 (dd, 1 H, *J* = 14, *J'* = 4 Hz), 1.67 (dd, 1 H, *J* = 6, *J'* = 4 Hz), 1.50-1.28 (complex, 7 H), 1.22 (s, 3 H, -C(C**H**$_3$)OH), 1.27-1.10

(complex, 3 H), 0.98 (s, 3 H, -CH_3) and 0.97 (s, 3 H, -CH_3); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 171.4 (p), 73.1 (p), 70.2 (p), 42.5 (p), 42.3 (a), 42.1 (p), 37.1 (p), 36.3 (p), 35.9 (p), 34.3 (p), 33.2 (a), 33.1 (a), 27.3 (a), 21.2 (a), 19.4 (p) and 18.1 (p); ir ($CHCl_3$ cast) 3480 (alcohol), 1737 and 1720 cm^{-1} (acetate); ms M^+ 268.2033 (calcd. for $C_{16}H_{28}O_3$: 268.2039).

(1R*, 6S*)-1-Acetoxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene (33) and (1R*, 6S*)-1-acetoxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene (34)



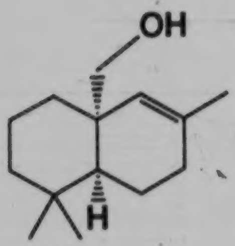
33



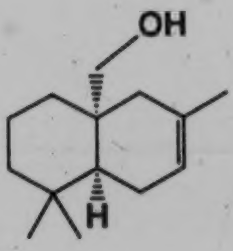
34

Hydroxy acetate **32** (1.39 g, 5.18 mmol) and 4-dimethylaminopyridine (3.16 g, 25.9 mmol) were dissolved in a solution of dry pyridine (55 mL). After cooling the solution to -40°C, phosphorus oxychloride (4.80 mL, 51.8 mmol) was added and the mixture allowed to react at -40°C for 12 h. The reaction was quenched with water (5 mL) and the resulting solution was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The organic extracts were combined, washed successively with 5 % HCl solution (3 x 20 mL), water (2 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated. A colorless oil which did not require further purification was obtained (1.25 g, 5.00 mmol, 97 %). It consisted of a mixture of inseparable acetates **33** and **34** in a ratio of 3 : 1 (ratio obtained by nmr area integration); ^1H nmr (300 MHz, $CDCl_3$) major isomer **33**: δ 5.05 (br s, 1 H, -C**H**=C(CH$_3$)-), 3.96 (d, 1 H, *J* = 10.5 Hz, -C**H**HOAc), 3.75 (d, 1 H, *J* = 10.5 Hz, -CH**H**OAc), 2.22 (br s, 1 H, -C**H**HC(CH$_3$)=), 2.16 (s, 1 H, -CH**H**C(CH$_3$)=), 2.05 (s, 3 H, -COC**H**$_3$), 1.62 (d, 3 H, *J* = 1 Hz, -C(C**H**$_3$)=CH-), 1.50-1.00 (complex, 9 H), 0.96 (s, 3 H, -C**H**$_3$) and 0.92 (s, 3 H, -C**H**$_3$); minor isomer **34**: δ 5.28 (br s, 1 H, -C(CH$_3$)=C**H**-), 3.87 (d, 1 H, *J* = 10.5 Hz, -C**H**HOAc), 3.78 (d, 1 H, *J* = 10.5 Hz, -CH**H**OAc), 2.24 (br s, 1 H, -C**H**HC(CH$_3$)=), 2.18 (s, 1 H, -CH**H**C(CH$_3$)=), 2.08 (s, 3 H, -COC**H**$_3$), 1.60 (d, 3 H, *J* = 1 Hz, -CH=C(C**H**$_3$)-), 0.92 (s, 3 H, -C**H**$_3$) and 0.83 (s, 3 H, -C**H**$_3$), other peaks were overlapped with those of the major isomer; ^{13}C nmr APT (75.5 MHz, $CDCl_3$): major isomer **33**: δ 171.3 (p), 137.0 (p), 120.5 (a), 71.4 (p), 41.6 (p), 41.5 (a), 35.4 (p), 34.7 (p), 34.3 (p), 33.9 (p), 32.6 (a), 23.5 (a), 23.4 (p), 21.7 (a), 21.0 (a) and 18.2 (p); minor isomer **34**: δ 171.4 (p), 131.2 (p), 119.9 (a), 72.2 (p), 42.2 (p), 36.1 (p), 33.8 (p), 33.4 (a), 23.6 (a) and 18.2 (p), other peaks were overlapped with those of the major isomer; ir ($CHCl_3$ cast) 1742 and 1235 cm^{-1} (-OAc); ms M^+ 250.1930 (calcd. for $C_{16}H_{26}O_2$: 250.1933).

(1R*, 6S*)-1-Hydroxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene (35) and (1R*, 6S*)-1-hydroxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-3-ene (26)



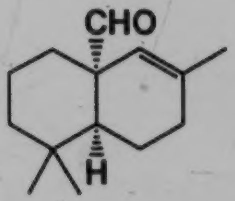
35



26

The mixture of acetates **33** and **34** (1.43 g, 5.70 mmol) was dissolved in methanol at room temperature and a saturated solution of potassium carbonate (15 mL) added. The mixture was refluxed for 2.5 h and then cooled. The methanol was evaporated under reduced pressure and the remaining aqueous solution was extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with water (2 x 10 mL) and brine (1 x 5 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the concentrate by flash chromatography (0-3 % ether and 1 % of 2-propanol in petroleum ether) gave alcohol **26** (270 mg, 1.29 mmol, 22 %) as a crystalline solid. This product was identical in all respects to the alcohol obtained by reduction of ester **24**. Further elution gave alcohol **35** (835 mg, 4.00 mmol, 70 %) as a colorless oil; ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.01 (br s, 1 H, -C**H**=C(CH_3)-), 3.43 (d, 1 H, J = 11 Hz, -C**H**HOH), 3.27 (d, 1 H, J = 11 Hz, -CH**H**OH), 1.94 (complex, 3 H), 1.80-1.70 (m, 1 H), 1.75 (s, 3 H, -CH=C(C**H**$_3$)-), 1.55-1.10 (complex, 8 H), 1.00 (s, 3 H, -C**H**$_3$) and 0.91 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, CDCl$_3$) δ 137.6 (p), 128.3 (a), 71.5 (p), 41.8 (a), 40.9 (p), 40.7 (p), 35.0 (p), 33.7 (p), 32.2 (a), 29.0 (p), 25.7 (a), 23.6 (a), 19.8 (p) and 19.2 (p); ir (CHCl$_3$ cast) 3256 cm^{-1}; ms M$^+$ 208.1827 (calcd. for $C_{14}H_{24}O$: 208.1828).

(1R*, 6S*)-1-Formyl-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene (36)

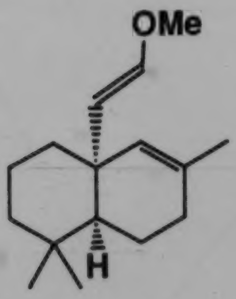


36

Pyridinium chlorochromate impregnated on alumina (0.9 mmol/g, 14.1 g, 12.7 mmol) was added to a solution of alcohol **35** (530 mg, 2.55 mmol) in dry dichloromethane (30 mL). The suspension was stirred at room temperature for 5 h. The mixture was filtered, concentrated, and the residue was purified by dry flash chromatography on Florisil (eluting with dichloromethane) to afford aldehyde **36** as a colorless oil (495 mg, 2.40 mmol, 94 %): ^{1}H nmr (300 MHz, CDCl$_3$) δ 9.27 (d, 1 H, J = 2 Hz, -C**H**O), 4.65 (br s, 1 H, -C**H**=C(CH$_3$)-), 2.15-1.95 (complex, 3 H), 1.86 (ddt, 1 H, J = 12, J' = 5, J'' = 2 Hz), 1.68 (s, 3 H, -CH=C(C**H**$_3$)-), 1.60-1.00 (complex, 7 H), 0.95 (s, 3 H, -C**H**$_3$) and 0.86 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, CDCl$_3$)

δ 204.4 (a), 139.5 (p), 121.9 (a), 53.7 (p), 44.6 (a), 34.6 (p), 33.4 (p), 31.3 (p), 30.2 (a), 28.2 (a), 27.8 (p), 23.7 (a), 20.0 (p) and 19.0 (p); ir ($CHCl_3$ cast) 2795, 2740 and 1719 cm^{-1} (CHO); ms M^+ 206.1665 (calcd. for $C_{14}H_{22}O$: 206.1670).

(1R*, 6S*)-1-((*E*)-2-Methoxyethenyl)-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene (37) and (1R*, 6S*)-1-((*Z*)-2-methoxyethenyl)-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene (38)



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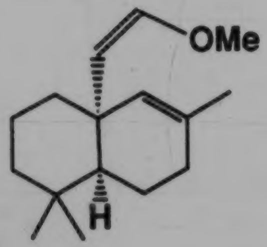
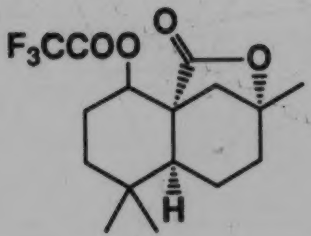


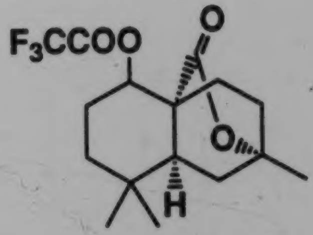
38

Potassium hydride (35 % dispersion in oil, 1.00 g, 8.78 mmol) was washed with ether (3 x 5 mL) under an argon atmosphere and then suspended in dry benzene (40 mL) at room temperature. Dimethyl sulfoxide (10 mL) was slowly added. When all the potassium hydride had reacted and the evolution of hydrogen had ceased, (methoxymethyl)triphenylphosphonium chloride (3.50 g, 10.2 mmol) was added. After 2 h of stirring, the solution developed a deep red-burgandy color. At this point aldehyde **36** (424 mg, 2.06 mmol) in a small amount of benzene was added. The reaction was stirred for an additional 2 h and then quenched with water (10 mL). The aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (1 x 5 mL) and brine (1 x 5 mL), dried ($MgSO_4$), filtered and concentrated. Bulb-to-bulb (70°C, 2.5 torr) distillation of the concentrate gave a colorless oil (452 mg, 1.93 mmol, 93 %) consisting of a 1 : 1 mixture of enol ethers as determined by nmr analysis. Purification by flash chromatography on silica gel (1 % triethylamine in petroleum ether) afforded *cis*-enol ether **38** as a colorless oil (205 mg): ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.64 (d, 1 H, *J* = 7 Hz, -CH=C**H**OCH$_3$), 5.12 (br s, 1 H, -C**H**=C(CH$_3$)-), 4.27 (d, 1 H, *J* = 7 Hz, -C**H**=CHOCH$_3$), 3.52 (s, 3 H, -OC**H**$_3$), 2.10-1.80 (complex, 3 H), 1.75 (ddd, 1 H, *J* = 13, *J'* = 6, *J''* = = 3 Hz), 1.62 (s, 3 H, -CH=C(C**H**$_3$)-), 1.56-1.20 (complex, 7 H), 1.11 (s, 3 H, -C**H**$_3$) and 0.89 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 143.9 (a), 131.6 (a), 129.9 (p), 118.2 (a), 59.6 (a), 48.3 (a), 40.7 (p), 36.5 (p), 34.0 (p), 33.5 (p), 31.0 (p), 30.9 (a), 30.8 (a), 23.4 (a), 21.3 (p), and 19.8 (p); ir ($CHCl_3$ cast) 1654 (C=C) and 1109 cm^{-1} (C-OCH$_3$); ms M$^+$ 234.1989 (calcd. for $C_{16}H_{26}O$: 234.1984). Continued elution gave *trans*-enol ether **37** as a colorless oil (195 mg): ^{1}H nmr (300 MHz, $CDCl_3$) δ 6.11 (d, 1 H, *J* = 13 Hz, -CH=C**H**OCH$_3$), 4.92 (br d, 1 H, *J* = 1.5 Hz, -C**H**=C(CH$_3$)-), 4.71 (d, 1 H, *J* = 13 Hz, -C**H**=CHOCH$_3$), 3.48 (s, 3 H, -OC**H**$_3$), 1.90-1.78 (m, 1 H), 1.62 (s, 3 H, -CH=C(C**H**$_3$)-), 1.60-1.05 (complex, 8 H), 1.02 (s, 3 H, -C**H**$_3$) and 0.89 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 146.1 (a), 132.7 (p), 131.4 (a), 116.3 (a), 56.0 (a), 49.3 (a), 38.9 (p), 36.4 (p), 34.0 (p), 31.9 (a), 29.9 (p), 28.2 (a), 23.4 (a), 20.5 (p) and 19.3 (p); ir ($CHCl_3$ cast) 1644 (C=C) and 1209 cm^{-1} ($C\text{-}OCH_3$); ms M^+ 234.1985 (calcd. for $C_{16}H_{26}O$: 234.1984).

(1R*, 4S*, 9R*)-8-Trifluoroacetyl-1,5,5-trimethyl-11-oxatricyclo[7.2.1.$0^{4,9}$]dodecan-10-one (39), (1S*, 3S*, 8R*)-7-trifluoroacetyl-1,4,4-trimethyl-10-oxatricyclo[6.2.2.$0^{3,8}$]dodecan-9-one (40), (1S*, 3S*, 7R*, 8R*)-8-carbomethoxy-1,4,4-trimethyl-11-oxatricyclo[5.3.1.$0^{3,8}$]undecane (41), and (1S*, 4S*, 8R*, 9R*)-9-carbomethoxy-1,5,5-trimethyl-11-oxatricyclo-[6,2,1,$0^{4,9}$]undecane (42).



39



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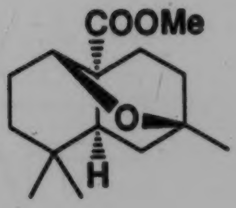
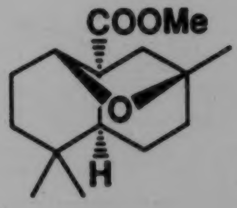


41

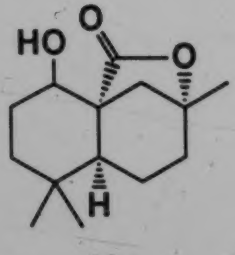


42

A mixture of isomeric keto esters **13** and **14** (1 : 1.75) (0.45 g, 1.80 mmol) was dissolved in CCl_4 (2 mL). Triethylsilane (0.86 mL, 5.42 mmol) and trifluoroacetic acid (1.39 mL, 18 mmol) were added, and the reaction mixture was refluxed for 9 h. The solution was cooled to room temperature, washed with water (3 x 2 mL) and brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the concentrate by flash chromatography on silica gel (0-5 % ether in petroleum ether) gave, in the following order of isolation, compounds **42** (85 mg, 29 %), **41** (106 mg, 36 %), **39** (100 mg, 65 %), and **40** (84 mg, 30 %). Yields are calculated from the original nmr ratio of the respective keto esters. Spectroscopic data obtained for these compounds are as follows. Compound **42**, a colorless oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.43 (t, 1 H, $J = J' = 2$ Hz, -C**H**O-), 3.66 (s, 3 H, -COOC**H**$_3$), 2.24 (dd, 1 H, $J = 2$, $J' = 1$ Hz), 1.90-1.40 (complex, 10 H), 1.30 (s, 3 H, -OC**H**$_3$), 0.90 (s, 3 H, -C**H**$_3$) and 0.82 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75 MHz, $CDCl_3$) δ 176.1 (p), 78.5 (p), 76.7 (a), 51.8 (a), 51.7 (p), 48.4 (p), 41.8 (a), 37.9 (p), 34.1 (p), 29.8 (a), 27.9 (p), 26.7 (a), 26.2 (a), 23.6 (p) and 20.2 (p); ir (neat) 1730 (ester) and 1250 (-C-O-) cm^{-1}; ms M$^+$ 252.1725 (calcd. for $C_{15}H_{24}O_3$: 252.1725). Compound **41**, a colorless oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.42 (br s, 1 H, -C**H**OC(CH$_3$)-), 3.68 (s, 3 H, -OC**H**$_3$), 2.28 (dd, 1 H, $J = 9$, $J' = 7$ Hz) 2.00-1.50 (complex, 9 H), 1.29 (s, 3 H, -C(C**H**$_3$)O-), 0.95 (dd, 1 H, $J = 14$, $J' = 5$ Hz), 0.89 (s, 3 H, -C**H**$_3$) and 0.82 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 176.0 (p), 74.8 (p), 76.6 (a), 51.8 (p), 51.6 (a), 48.3 (p), 41.8 (a), 37.9 (p), 34.0 (p), 29.8 (a), 27.8 (p), 26.6 (a), 26.1 (a), 23.5 (p) and 20.1 (a); ir (neat) 1729 (ester) and 1250 (ether) cm^{-1}; ms M$^+$ 252.1727 (calcd. for $C_{15}H_{24}O_3$: 252.1727). Compound **39**, white crystals:

m.p. 132-133°C (petroleum ether); ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.22 (dd, 1 H, $J = 11$, $J' = 4$ Hz, $-C\mathbf{H}OOCCF_3$), 2.24 (d, 1 H, $J = 11$ Hz, $-CC\mathbf{H}HC(CH_3)O-$), 2.11 (d, 1 H, $J = 11$ Hz $-CCH\mathbf{H}C(CH_3)O-$), 2.03 (m, 1 H, $-C\mathbf{H}HCHOOCF_3$), 1.92-1.75 (complex, 3 H), 1.52 (s, 3 H, $-C(C\mathbf{H}_3)O-$), 1.68-1.43 (complex, 5 H), 1.07 (s, 3 H, $-CH_3$) and 0.98 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 177.1, 118.7, 82.9, 76.9, 53.5, 42.8, 38.1, 36.8, 34.2, 33.5, 32.3, 25.2, 24.6, 22.7 and 19.5; ir ($CHCl_3$ cast) 1789 (ester) and 1770 (lactone) cm^{-1}; ms M$^+$ 334.1390 (calcd. for $C_{16}H_{21}F_3O_4$: 334.1386); Anal. calcd. for $C_{16}H_{21}F_3O_4$: C, 57.46; H, 6.33; found: C, 57.77; H, 6.51. Compound **40**, a colorless oil: ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.42 (dd, 1 H, $J = 12$, $J' = 5$ Hz, $-C\mathbf{H}OOCCF_3$), 2.40-1.20 (complex, 11 H), 1.44 (s, 3 H, $-C(C\mathbf{H}_3)O-$), 1.09 (s, 3 H, $-C\mathbf{H}_3$) and 0.89 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 175.1 (p), 116.5 (p), 112.7 (p), 80.9 (p), 76.6 (a), 44.1 (p), 43.7 (a), 37.9 (p), 34.1 (p), 33.4 (p), 31.6 (a), 31.3 (p), 25.6 (a), 23.2 (p), 20.5 (a) and 18.4 (p); ir ($CHCl_3$ cast) 1784 (ester) and 1739 cm^{-1} (lactone); ms M$^+$ 334.1390 (calcd. for $C_{16}H_{21}F_3O_4$: 334.1386).

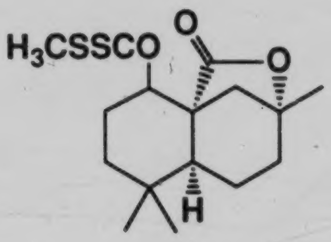
(1R*, 4S*, 9R*)-8-Hydroxy-1,5,5-trimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecan-10-one (43).



43

Trifluoroacetate ester **39** (500 mg, 1.5 mmol) was dissolved in methanol (5 mL). Sodium methoxide (122 mg, 2.25 mmol) was added and the mixture stirred at room temperature overnight (~10 h). After quenching the reaction with water, the solution was extracted with ethyl acetate (3 x 3 mL). The extracts were combined and washed successively with 5 % HCl (1 x 3 mL), water (1 x 3 mL), and brine (1 x 2 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated. Upon crystallization from ether, white crystals of **43** were obtained (350 mg, 98 %): m.p. 120°C (it starts subliming at ~105°C); ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.79 (dd, 1 H, J = 11, J' = 4 Hz, -C**H**OH), 2.96 (br s, 1 H, -O**H**), 2.11 (d, 1 H, J = 11 Hz, -CC**H**HC(CH_3)O-), 1.92 (d, 1 H, J = 11 Hz, -CCH**H**C(CH_3)O-), 1.80-1.10 (complex, 9 H), 1.37 (s, 3 H, -C(C**H**$_3$)O-), 0.90 (s, 3 H, -C**H**$_3$) and 0.82 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 180.1 (p), 83.2 (p), 70.2 (a), 55.9 (p), 42.6 (a), 38.8 (p), 35.6 (p), 34.1 (p), 33.8 (p), 32.6 (a), 27.8 (p), 25.2 (a), 22.8 (a) and 19.7 (p); ir ($CHCl_3$ cast) 3470 (-OH), 1773 and 1757 cm^{-1} (lactone); ms M$^+$ 238.1571 (calcd. for $C_{14}H_{22}O_3$: 238.1563). Anal. calcd. for $C_{14}H_{22}O_3$: C, 70.54; H, 9.31; found: C, 70.64; H, 9.48.

(1R*, 4S*, 9R*)-8-(Methylmercaptothiocarbonyloxy)-1,5,5-trimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecan-10-one (44).

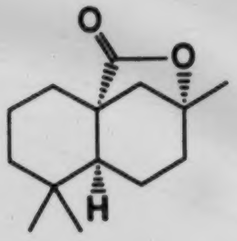


44

Hydroxy lactone **43** (205 mg, 0.86 mmol) was dissolved in 1,2-dimethoxyethane under an argon atmosphere. Sodium hydride (130 mg of a 80 % dispersion in mineral oil, 4.3 mmol) was added slowly with stirring. After 20 min, carbon disulfide (0.52 mL 8.6 mmol) and methyl iodide (0.27 mL, 4.3 mmol) were added. The solution was stirred for 10 h, then the reaction mixture was poured into ice-water. The aqueous layer was extracted with ether (3 x 3 mL). The organic extracts were combined, washed successively with 10 % NaOH (1 x 2 mL), bleach (2 x 2 mL), water (1 x 2 mL) and brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated to give a colorless oil (173 mg, 0.53 mmol, 61 %). After crystallization from ethyl acetate-petroleum ether, white crystals were obtained: m.p. 180-181°C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.77 (dd, 1 H,

J = 9, J' = 4 Hz, -C**H**OCSSCH$_3$), 2.52 (s, 3 H, -SC**H**$_3$), 2.32-2.10 (complex, 3 H), 1.90-1.70 (complex, 3 H), 1.70-1.30 (complex, 5 H), 1.50 (s, 3 H, -C(C**H**$_3$)O-), 1.06 (s, 3 H, -C**H**$_3$) and 0.97 (s, 3 H, -C**H**$_3$); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 214.5, 177.6, 82.9, 81.3, 53.9, 42.9, 38.1, 37.7, 34.3, 33.6, 32.3, 25.3, 24.1, 22.7, 19.6 and 19.0; ir (CHCl$_3$ cast) 1775 (lactone), 1224, and 1062 cm^{-1} (xanthate); ms M$^+$ 328.1169 (calcd. for $C_{16}H_{24}O_3S_2$: 328.1159). Anal. calcd. for $C_{16}H_{24}O_3S_2$: C, 58.51; H, 7.37; found: C, 58.38; H, 7.47.

(1R*, 4S*, 9R*)-1,5,5-Trimethyl-11-oxatricyclo[7.2.1.0^{4,9}]-dodecan-10-one (30) and (1R*, 3S*, 8R*)-1,4,4-trimethyl-10-oxatricyclo[6.2.2.0^{3,8}]dodecan-9-one (45)



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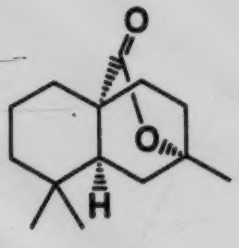

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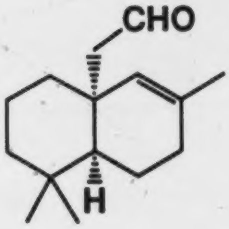
A mixture of isomeric keto esters **24** and **25** (1 : 1, 27 mg, 0.96 mmol) was dissolved in benzene. *p*-Toluenesulfonic acid monohydrate (500 mg, 2.6 mmol) was added and the reaction flask connected to a Dean-Stark apparatus for water removal. The solution was refluxed for 3 h and then cooled down to room temperature. The organic layer was washed successively with water (2 x 2 mL), saturated sodium bicarbonate solution (2 x 3 mL), water (1 x 2 mL) and brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the concentrate by flash chromatography on silica gel (0-15 % ether in petroleum ether) gave white crystals (87 mg, 0.39 mmol, 41 %) of lactone **30** identical with an authentic sample obtained previously from pure ester **24**. Further elution gave lactone **45** as a colorless oil (89 mg, 0.40 mmol, 42 %); ^1H nmr (400 MHz, $CDCl_3$) δ 2.38 (ddd, 1 H, J = 14, J' = 12.5, J''' = 4 Hz), 1.95-1.30 (complex, 11 H), 1.42 (s, 3 H, $-C(CH_3)O-$), 1.16 (dt, 1 H, J = 13, J' =J'' = 5 Hz), 1.04 (s, 3 H, $-CH_3$) and 0.86 (s, 3 H, $-CH_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 178.9 (p), 80.5 (p), 43.5 (a), 40.6 (p), 40.5 (p), 34.2 (p), 33.9 (p), 32.5 (a), 32.1 (p), 30.6 (p), 25.6 (a), 24.5 (p), 20.7 (a) and 17.9 (p); ir ($CHCl_3$ cast) 1734 cm^{-1} (lactone); ms M^+ 222.1616 (calcd. for $C_{14}H_{22}O_2$: 222.1619).

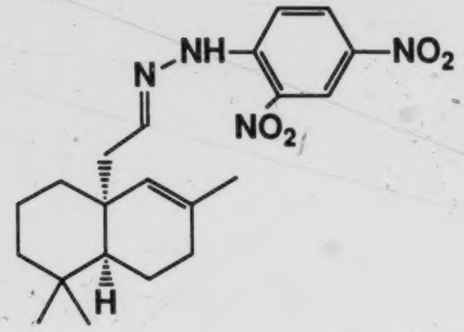
(1R*, 6S*)-1-(2-Oxoethyl)-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene ((±)-Isoacanthodoral) (3).



3

A column containing silica gel was eluted with a petroleum ether solution containing 1 % acetic acid and 1 % water. A mixture of enol ethers **30** and **31** (25 mg, 0.107 mmol) was placed in the column and eluted slightly. The column was allowed to stand for 24 h. Elution with 0-5 % ether in petroleum ether afforded (±)-isoacanthodoral (23 mg, 0.104 mmol, 97 %) as a colorless fragrant oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 9.73 (dd, 1 H, $J = J' = 3$ Hz, -C**H**O), 5.23 (d, 1 H, $J = 1$ Hz, -C**H**=C(CH_3)-), 2.71 (dd, 1 H, $J = 15$, $J' = 3$ Hz, -C**H**HCHO), 2.13 (dd, 1 H, $J = 15$, $J' = 3$ Hz, -CH**H**CHO), 2.00-1.70 (complex, 4 H), 1.65 (s, 3 H, -CH=C(C**H**$_3$)-), 1.50-1.11 (complex, 7 H), 1.00 (s, 3 H, -C**H**$_3$) and 0.91 (s, 3 H, -C**H**$_3$); ^{13}C nmr DEPT (75.5 MHz, $CDCl_3$) δ 204.8 (d), 135.5 (s), 129.9 (d), 57.2 (t), 46.3 (d), 40.1 (t), 38.5 (t), 38.2 (s), 34.2 (s), 32.4 (q), 28.9 (t), 26.4 (q), 23.5 (q), 19.9 (t) and 19.2 (t); ir ($CHCl_3$ cast) 2845, 2720 and 1720 cm^{-1} (CHO); ms M^+ 220.1821 (calcd. for $C_{15}H_{24}O$: 220.1827).

(1R*, 6S*)-1-(2-Oxoethyl)-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene 2,4-dinitrophenylhydrazone (8)



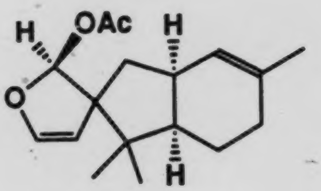
8

Aldehyde **3** (20 mg, 0.09 mmol) was dissolved in ethanol (0.5 mL). A 3 % solution of 2,4-dinitrophenylhydrazine in water, ethanol and H_2SO_4 (2 : 7 : 2) (1 mL, 0.15 mmol) was added and the resulting mixture was stirred for 3 h. After addition of H_2O (2 mL), the aqueous layer was extracted with dichloromethane (3 x 3 mL). The organic extracts were washed with H_2O (2 x 1 mL) and brine (1 x 1 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The orange residue was redissolved in dichloromethane, and petroleum ether added to precipitate a red solid. The precipitate was filtered off and the filtrate passed through Florisil with petroleum ether elution. The solution was concentrated to a residual oil, which was purified by flash chromatography on silica gel (0-5 % ether in petroleum ether). Recrystallization of the 2,4-DNP derivative (28.8 mg, 80 %) from ether-petroleum ether gave orange needles. The following physical properties of this compound were found to be identical with those reported for the 2,4-DNP derivative of the naturally occurring isoacanthodoral: m.p. 144-146°C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 11.02 (br s, 1 H, -CH=N-N**H**-), 9.12 (d, 1 H, *J* = 2.5 Hz), 8.29 (ddd, 1 H, *J* = 9.5, *J'* = 2.5, *J''* = 1 Hz), 7.93 (d, 1 H, *J* = 9.5 Hz), 7.46 (t, 1 H, *J* =*J'* = 6 Hz), 5.14 (br s, 1 H, -C**H**=C(CH_3)-), 2.79 (dd, 1 H, *J* = 14, *J'* = 6 Hz), 2.24 (dd, 1 H, *J* = 14, *J'* = 6 Hz), 1.95 (m, 3 H), 1.75 (m, 1 H), 1.67 (s, 3 H), 1.60-1.10 (complex, 7 H), 1.04 (s, 3 H, -C**H**$_3$) and 0.91 (s, 3 H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 152.1 (a), 145.2 (p), 137.8 (p), 135.5 (p), 130.3 (a), 130.0 (a), 128.8 (p), 123.6 (a), 116.6 (a), 46.5 (p), 45.8 (a), 40.2 (p), 38.9 (p), 38.2 (p), 34.3 (p), 32.3 (a), 28.9 (p), 26.5 (a), 23.5 (a), 19.9 (p) and 19.2 (p); ir ($CHCl_3$ cast) 3302 (NH), 1618 (C=N), 1516 (NO_2) cm^{-1}; ms M$^+$ 400.2116 (calcd. for $C_{21}H_{28}N_4O_4$: 400.2110). Anal. calcd. for $C_{21}H_{28}N_4O_4$: C, 62.79; H, 7.05; N, 14.00; found: C, 62.38; H, 7.05; N, 13.65.

Chapter 2

Towards the Synthesis of Spirodysin

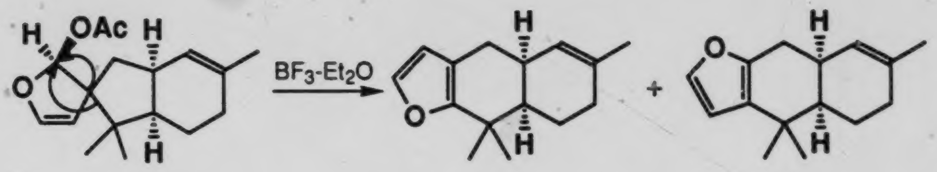
Spirodysin **46** is a sesquiterpene acetate which was isolated from the sponge *Dysidea herbacea* collected from the Gladstone area of Queensland, Australia.[57] The extraction gave spirodysin in a 0.3 % yield based on the dry weight of the sponge. Its structural assignment was based upon analysis of its proton and carbon nmr spectra including the use of lanthanide shift reagents.



46

The stereochemistry at the spiro ring junction could not be determined with these techniques, although an nOe of 20 % between the proton adjacent to the acetate group and one of the methyl groups, allowed the assignment of the acetoxyl group *anti* to the *gem*-dimethyl group. The assignment was supported by the shifting effects produced by Eu(fod)$_3$ and Pr(fod)$_3$ on carbons and protons in proximity to the acetate group.

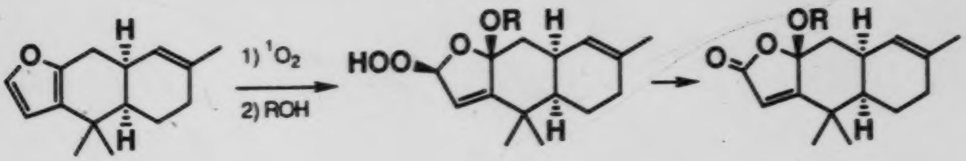
Spirodysin is a metabolite of the sponge, which is transformed into different compounds by the sponge. Several nudibranchs sequester and use these compounds to produce chemicals for their defence system. Wells[58] proposed that spirodysin could be a precursor of a series of furanoid sesquiterpenes previously isolated from other sources. This proposal was supported when spirodysin was transformed by $BF_3{\bullet}Et_2O$ to a 1 : 1 mixture of the furanoids furodysin **47** and furodysinin **48**, both of which have been isolated[58] from a freeze dried sponge of the genus *Dysidea*.



46 **47** **48**

Faulkner[59] studied the nudibranch *Chromodoris funerea* and suggested that these furanoid sesquiterpenes are precursors for the defense chemicals of the animal. As the sea slug is unable to produce these chemicals itself, it acquires furodysin (**47**) and furodysinin (**48**) from the sponge and oxidizes them into a compound (possibly an endoperoxide) which proved to be unstable to the extraction conditions. The oxidized compound reacted with the solvent. When an extraction of the animal was performed in methanol, a 1 : 1 mixture of hydroperoxide **49** (R = CH_3) and lactone **50** (R = CH_3) was obtained. Each of compounds **49** and **50** showed a stronger antifeedant activity than the parent compound furodysinin.

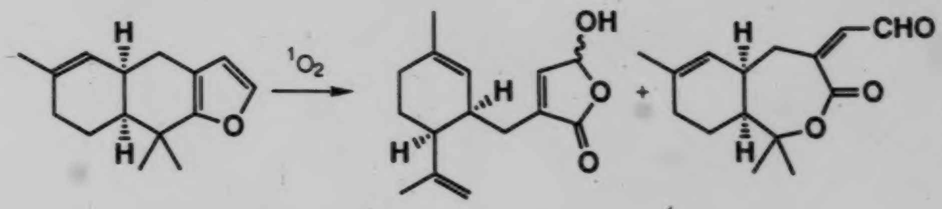
To prove this hypothesis, pure furodysinin (**48**) was photooxygenated at -78°C with singlet oxygen generated using rose bengal as sensitizer. A 77 % yield of *O*-methylfurodysinin hydroperoxide (**49**, R = CH_3) was obtained. On prolonged storage or upon heating, the hydroperoxide oxidized slowly to the methoxy lactone (**50**, R = CH_3). A faster conversion of hydroperoxide to the lactone took place when the hydroperoxide was treated with manganese dioxide in ether.



48 **49** **50**

Furodysin (**47**) is also oxidized by singlet oxygen to γ-hydroxybutenolide **51** and lactone **52** in a 2 : 1 ratio. It has been proposed[59] that the oxidation of compound **47** also proceeds by the formation of an endoperoxide, followed by ring cleavage. Although these two compounds have been isolated from a nudibranch, no antifeedant activity was observed for either of them, indicating that the defense chemical used by the nudibranch might be the endoperoxide itself.

Since spirodysin is a precursor of furodysinin and furodysin, a total synthesis of the three compounds could be achieved if a synthesis of spirodysin is developed.

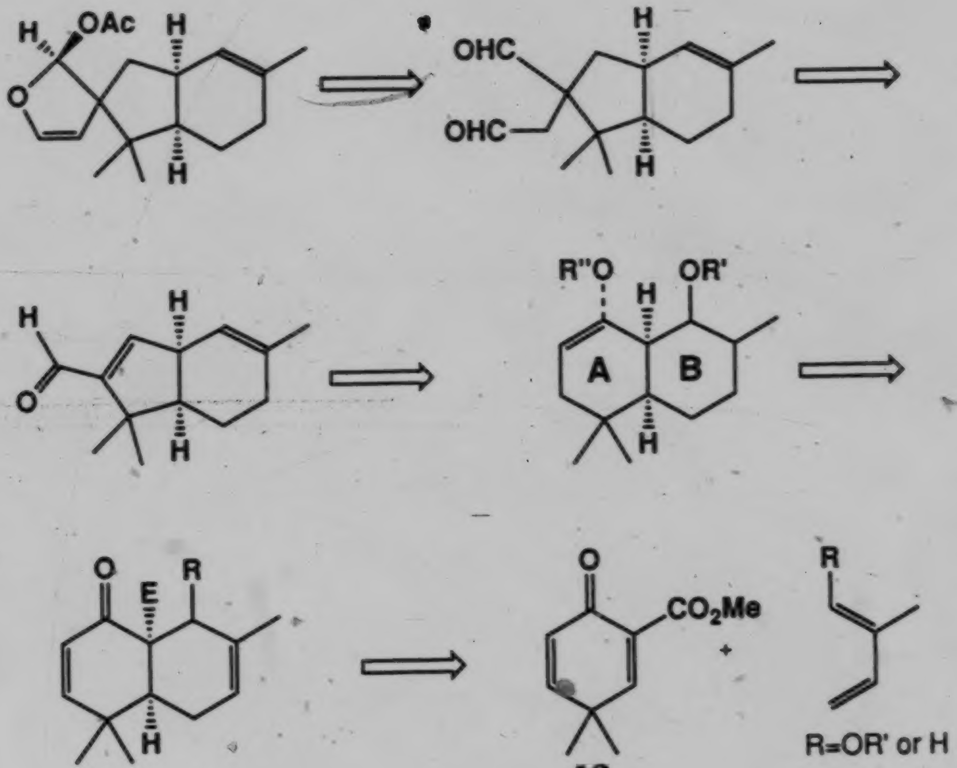


47 **51** **52**

Two approaches to the synthesis of spirodysin **46** could be envisioned. The first (Scheme 4) employs a dienophile such as **12** in a Diels-Alder cycloaddition to build a 6,6-bicyclic system similar to that used in the synthesis of isoacanthodoral described in Chapter 1 of this thesis. The diene used in this case should be functionalized at the C-1 position in order to facilitate the formation of the double bond at the required position at a late stage in the synthesis.

After the 6,6-bicyclic system has been formed the "A-ring" must be contracted to a 5-membered ring. Ring contractions can be carried out through an oxidative cleavage of a double bond in the molecule, followed by an intramolecular aldol reaction of the resulting dicarbonyl compound, to form a contracted ring with an α,β-unsaturated carbonyl. Opening of a 6-membered ring at a specific position can also be done by the oxidative cleavage of an activated double bond (enamine,[60, 61, 62] silyl enol ether[62]) or via the oxidative cleavage of an α-hydroxy ketone or a 1,2-diketone.

Scheme 4

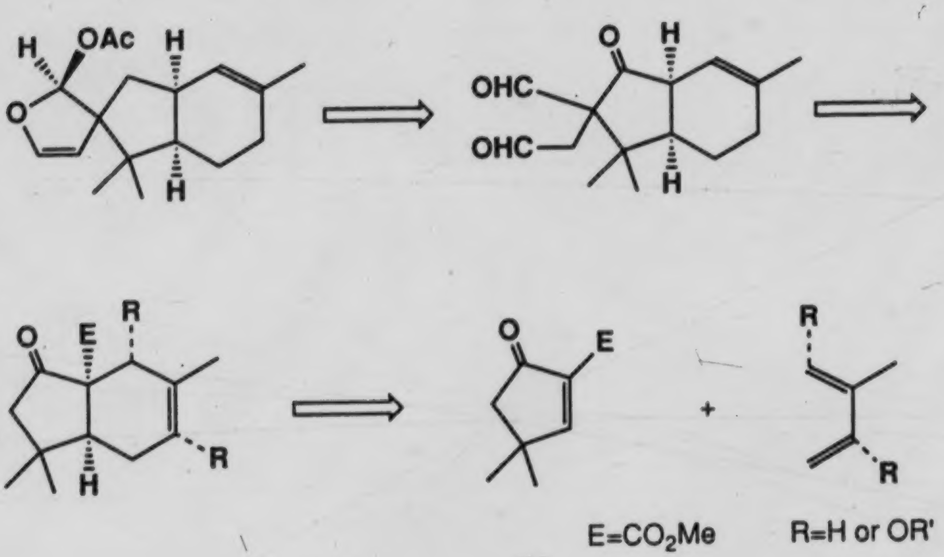


12

Formation of a double bond between C-2 and C-3 of the Diels-Alder adduct (Scheme 4) could provide a system suitable for a ring contraction. Ozonolysis of the double bond to the dialdehyde, followed by aldol reaction, could lead to the desired 5,6-bicyclic system required for the synthesis of spirodysin. Reduction of the double bond of the α,β-unsaturated aldehyde and *in situ* alkylation of the resultant enolate could furnish the required functionalities for the formation of the spiro ring.

Some difficulties can be foreseen in this synthetic scheme. The selective cleavage of the double bond between C-2 and C-3 in the presence of another double bond may be difficult. Some selectivity has been observed when the bond to be cleaved is activated by an electron donating group (e. g. enol ether and enamine), since the electron donating group will direct the oxidizing agent to this bond. The selective cleavage reaction can also be avoided if a diene activated at C-1 is used during the cycloaddition reaction with dienophile **12**. In this case both double bonds in the Diels-Alder adduct could be reduced by hydrogenation. Subsequent formation of a double bond between C-2 and C-3 and cleavage to the dialdehyde would probably occur without problems. However, if a diene activated at C-1 is used a different problem may arise. The Diels-Alder adduct obtained will have this activating group in a β-position with respect to the β-keto ester of the original dienophile. It is necessary to eliminate the carbomethoxyl group from the system before the final product is reached, but decarbomethoxylation will produce an enolate which could induce the elimination of the activating group to give an α,β-unsaturated ketone and destroy the functionality originally introduced to control the position of the final double bond. Nevertheless, C-1 (diene) activation may be an advantage because the double bond formed in the later stage will be attached to a bridge-head carbon, bringing the possibility that the double bond may isomerize to the adjacent desired position.

Scheme 5



53

In the second approach the 5,6-bicyclic system could be formed directly via a Diels-Alder reaction of dienophile **53** with a suitable diene (Scheme 5). The diene could be functionalized at C-1 or at C-3 or at both positions (C-1 and C-3). If a C-3 functionalized diene is used for the Diels-Alder reaction the enol ether generated could be converted to an α-halo or α-hydroxy ketone, which could be dehalogenated or dehydrated to produce an α,β-unsaturated ketone, fixing the double bond at the desired position. The α,β-unsaturated ketone in the six-membered ring can also be generated by the use of an analog of Danishefsky's diene, followed by hydrolysis of the adduct. Danishefsky-type dienes are functionalized at C-1 and at C-3, making them highly regioselective in the addition to the dienophile. The strategy through an α,β-unsaturated ketone seems to be the most reasonable approach because it will place the double bond in the required position. Selective protection of the enone carbonyl, would allow the alkylation at the methylene carbon alpha to the cyclopentanone moiety. Generation of a dialdehyde, cyclization and trapping of the hemiacetal thus formed would lead to a system which only requires the removal of the carbonyl moieties and the carbomethoxy group to complete the synthesis. The only problem that can be envisioned is the selective reduction of the ketone carbonyls in the presence of the double bond. This approach is also interesting because little is known about the Diels-Alder reaction of cyclopentenones such as **53**.[63] A study of these cycloadditions will allow for comparison with six-membered ring systems which have already been studied extensively.[2, 14, 64]

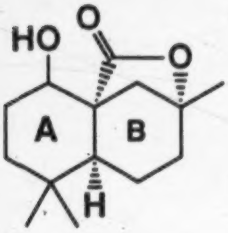
No matter what approach is used for the construction of the 5,6-bicyclic system, the spiro ring of spirodysin has to be formed through alkylation at the α-position of a carbonyl in the 5-membered ring. There is a potential problem with this alkylation. It will have to take place next to the *gem*-dimethyl group, a very hindered carbon. After the dialkylation has taken place and a dialdehyde has been formed, the formation of the final acetal should be rather straight forward.

Results and Discussion

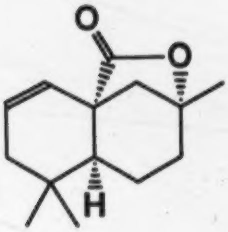
The synthesis of isoacanthadoral (**3**) described in the previous chapter of this work gave us experience in working with 6,6-bicyclic systems. Based on this experience, we decided to undertake the first synthetic approach to spirodysin (**46**).

Hydroxy lactone **43** contains proper functionalities as a substrate in the ring contraction approach. The double bond in the B-ring has been masked with a "protected" hydroxyl group. Ring A has an alcohol moiety at C-2 which may be eliminated to form a double bond at the position required for the ring contraction reaction sequence. Therefore, it is necessary to find a method for double bond formation and cleavage in the presence of the lactone ring.

Copper(II) sulfate impregnated on silica[47, 48, 65] has been reported to dehydrate tertiary alcohols and certain secondary alcohols under neutral conditions. When a slurry of the alcohol and copper sulfate on silica are refluxed in benzene, toluene or xylenes an olefin is readily obtained simply by filtration of the slurry and concentration of the filtrate.



43



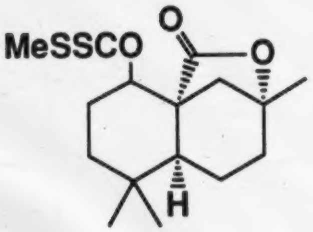
54

Compound **43** was refluxed in benzene in the presence of copper(II) sulfate impregnated on silica. After 30 h at 80°C no reaction had taken place and hydroxy lactone **43** was recovered. When the solvent was changed to toluene and similar reaction conditions (30 h, 110°C) were applied to the hydroxy lactone again only the starting material was recovered. Attempts to dehydrate the molecule in xylenes resulted in complete decomposition of the hydroxy lactone **43** after refluxing the solution for 4 h. The ^{1}H nmr spectrum of the resulting crude oil did not display any olefinic hydrogen, indicating that compound **54** was not produced. It is difficult to speculate what happened during the high temperature treatment of compound **43** with copper(II) sulfate. The mechanism of the dehydration with copper(II) sulfate has been proposed to proceed by elimination of water followed by carbocation formation at the carbon where the hydroxyl group was originally attached. Once a carbocation is formed from compound **43** a number of rearrangements could take place, especially when the reaction is carried out at high temperature.

Another method was sought for the formation of the double bond which would avoid the formation of a carbocation intermediate during the dehydration reaction. Hydroxy lactone **43** was reacted with thionyl chloride in pyridine. No reaction was observed and only starting material was recovered after 24 h of stirring the solution at room temperature. When the temperature was increased to 40°C complete decomposition of compound **43** took place within 1 h. Reaction of hydroxy lactone **43** with phosphorus oxychloride in pyridine at room temperature resulted in rapid decomposition of the starting material.

The hydroxy group in compound **43** is in an equatorial position (the hydrogen adjacent to the hydroxyl group appears in the ^{1}H nmr spectrum as a doublet of doublets with coupling constants of 11 and 4 Hz. Obviously the dehydration with $SOCl_2$ and $POCl_3$ of an equatorial hydroxyl is difficult since these reagents require an *anti*-periplanar configuration for the elimination. If the hydroxyl group adopts an axial position it will cause the bicyclic system to have an increase in the ring strain. Hydroxy lactone **43** is already highly strained because of the presence of the lactone ring which holds the B-ring of the fused bicyclic system in a boat conformation. Since the axial conformation of the hydroxyl group is unfavorable it is unlikely that it will be formed. Because an *anti*-elimination reaction was not feasible with hydroxy lactone **43** we decided to attempt a *syn*-elimination reaction.

Alcohol derivatives such as esters, xanthates and carbamates undergo *syn*-elimination[66] when they are pyrolyzed. During the synthesis of isoacanthodoral the methyl xanthate **44** was prepared from hydroxy lactone **43**. Compound **44** was pyrolyzed (190°C) under vacuum (0.5 mm Hg). Heating the crystals in a bulb-to-bulb distillation apparatus (Kugelrohr) gave recovered starting material. Increasing the pressure in the system to 200 mm Hg, gave the same results. When the pyrolysis was performed at atmospheric pressure no change was observed. Only the starting compound **44** distilled over, even when the distillation took 5 h at 190°C. Compound **44** proved to be very stable to the reaction conditions.



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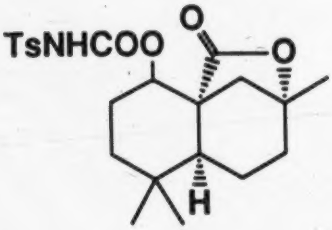
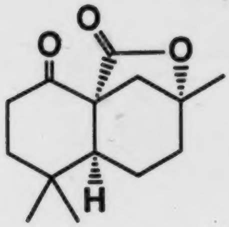


55

Tosyl carbamates also react upon pyrolysis via the *syn*-elimination mechanism to form olefins. Carbamate **55** was formed by the addition of *p*-toluenesulfonyl isocyanate, in the presence of a catalytic amount of sodium hydride, to a solution of hydroxy lactone **43** in dry benzene. The ^{1}H nmr spectrum of carbamate **55** displays aromatic hydrogen signals at δ 7.81 (d, J = 8 Hz, 2 H) and 7.31 (J = 8 Hz, 2 H). The hydrogen attached to the nitrogen atom appears at δ 4.87 (br s, 1 H) and the H-8 is displayed at δ 3.94 (dd, $J = 12$, $J' = 4$ Hz). Four methyl singlets appear at δ 2.45 (ArC**H**$_3$), 1.50 (C-1), 1.03 and 0.95 (*gem*-dimethyl). The infrared spectrum of compound **55** shows a weak, broad absorption at 3200 cm^{-1} (N-H), as well as a strong, broad carbonyl adsorption at 1750 cm^{-1} (carbamate and lactone), while the presence of an aromatic ring was indicated by absorption bands at 885 and 547 cm^{-1}. High resolution mass spectrometry failed to give a molecular ion peak at 371.2096 (calcd. for $C_{22}H_{29}O_4N$). Instead it gave a peak at m/z 238.1567 ($C_{14}H_{22}O_3$), indicating that the molecule lost the tolyl group upon bombardment. Pyrolysis of compound **55** at 180°C and atmospheric pressure (700 mm Hg) gave no indication of the formation of an olefin. Only distilled starting material was recovered.

Elimination reactions are limited by the requirement that the substrate adopt a specific orientation during the transition state. If the formation of the transition state is restricted then the elimination does not occur at all or the reaction takes a different course. For example, substitution or an intramolecular rearrangement of the molecule may occur in place of elimination. It appears that the lactone of compound **43** is forcing the molecule into a certain conformation, preventing the molecule from adopting the required conformation for elimination. Examination of Dreiding molecular models shows an increase in the ring strain upon introduction of a double bond in the A-ring. The double bond flattens the A-ring transmitting a great deal of strain to the B-ring which is already strained by the lactone group.

A different method to form the double bond in the A-ring is through formation of an enol ether. Once the double bond is in place the ozonolysis reaction should not present a serious problem. Hydroxy lactone **43** was oxidized in dichoromethane solution with pyridinium chlorochromate impregnated on alumina.[40] Keto lactone **56** was obtained in 90 % yield after filtration of the slurry through Florisil and concentration of the resulting filtrate. The infrared spectrum of keto lactone **56** displays two carbonyl absorptions at 1779 (lactone) and 1706 cm^{-1} (ketone). The ^1H nmr spectrum shows two separate signals for the hydrogens alpha to the ketone at δ 2.65 (ddd, $J = 18$, $J' = 7$, $J'' = 5$ Hz) and 2.42 (ddd, $J = 18$, $J' = 9$, $J'' = 7$ Hz). As well, methyl singlets are displayed at δ 1.50 (C-9), 1.05 and 1.00 (*gem*-dimethyl). The ^{13}C nmr DEPT spectrum shows two carbonyl singlets at δ 207.8 (ketone) and 176.0 (lactone), as well as another singlet at δ 83.7 for the carbon (C-9) bearing the oxygen of the lactone. High resolution mass spectrometry gave a molecular ion peak at m/z 236.1415 consistent with the molecular formula $C_{14}H_{20}O_3$.

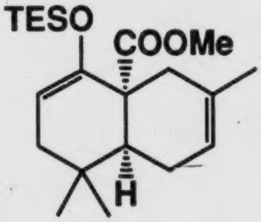


56

The enolate of compound **56** was formed using lithium diisopropylamide in tetrahydrofuran. Attempts to trap the enolate in the presence of trimethylsilyl chloride failed. Following the progress of the reaction by thin layer chromatography (tlc), it showed that the starting material had been consumed after 2 h of reaction and a less polar component was formed. This second component vanished upon addition of water to the reaction as indicated by tlc of the reaction mixture. Presumably some trimethylsilyl enol ether was formed, but it hydrolyzed back to the ketone group when water was present in the reaction, probably to relieve the highly strained system formed. Unfortunately, the ring contraction approach through the olefin lactone **54** did not produce any useful product which could be subjected to ozonolysis. As the formation of the double bond between C-2 and C-3 failed when the system contains the lactone moiety, such as in compound **56**, it was necessary to undertake a different approach to the cleavage of the A-ring.

Another way to induce the cleavage at that particular position (between C-2 and C-3) would be through the introduction of a hydroxy group or via oxidation of the alpha position to a carbonyl, followed by cleavage of the α-hydroxy ketone or the 1,2-diketone.

Formation of α-hydroxy ketones can be carried out via epoxidation on an enol ether.[67] Selective epoxidation of silyl enol ether, in the presence of isolated double bond, has been carried out with an equimolar amount of 3-chloroperoxybenzoic acid. In the synthesis of isoacanthodoral the triethylsilyl enol ether **15** was formed. This compound was subjected to epoxidation at -10°C with 3-chloroperbenzoic acid (1 eq). A mixture of compounds was formed. At least six components could be observed by tlc analysis of the reaction mixture. Attempts made to separate this mixture did not produce any desired results.

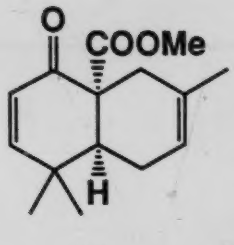


15

Molybdenyl acetylacetonate, when used in the presence of anhydrous *t*-butyl hydroperoxide, catalyzes the cleavage of activated double bonds to furnish dicarboxylic acids.[62] This cleavage can be carried out in the presence of isolated double bond. Treatment of triethylsilyl enol ether **15** with *t*-butyl hydroperoxide in the presence of molybdenyl acetylacetonate in a benzene solution resulted in complete decomposition of the starting material. Neither acid nor epoxide nor hydroxy ketone were detected in the reaction mixture.

Attempted use of an α-hydroxy ketone intermediate to effect cleavage of the A-ring did not work with enol ether **15**. Possibly the acidity of the 3-chlorobenzoic acid produced during the epoxidation reactions caused side reaction to occur at the C-8 double bond as previously observed for the similar system (Chapter 1).

An alternative synthetic route to the formation of an α-hydroxy ketone or a 1,2-diketone is through the formation of an epoxide at the double bond of an α,β-unsaturated ketone, followed by a reduction at the β-position. Traditionally, selective formation of an epoxide of the enone double bond in the presence of an isolated double bond is carried out by treatment with hydrogen peroxide in the presence of sodium hydroxide. A more selective method for the formation of epoxides at the double bond of α,β-unsaturated ketones employs anhydrous *t*-butyl hydroperoxide in the presence of benzyltrimethylammonium hydroxide (Triton B).[68] The latter method has the disadvantage that anhydrous *t*-butyl hydroperoxide can react explosively if not handled properly.[69]



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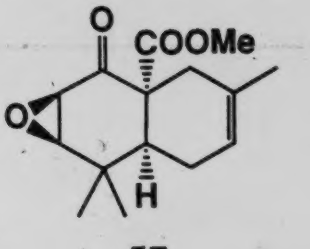


57

In the synthesis of isoacanthodoral the intermediate Diels-Alder adduct **14** (Chapter 1) contained the proper functionality with the required system for epoxide formation. Thus, treatment of keto ester **14** with hydrogen peroxide in the presence of sodium hydroxide at 0°C in methanol gave 15 % of the desired epoxyketone **57** after 24 h. The remaining material was transformed into a mixture of unidentifiable products.

When keto ester **14** was treated with *t*-butyl hydroperoxide in the presence of Triton B, epoxyketone **57** was obtained as a colorless oil in 91 % yield. The infrared spectrum of compound **57** displays strong absorptions at 1746 (ester) and 1719 cm^{-1} (ketone) and medium absorption at 1708 (olefin) and 1225 cm^{-1} (oxirane stretching). The ^{1}H nmr spectrum shows the C-8 vinylic hydrogen as a broad doublet of doublets at δ 5.42 with coupling constants of 5 Hz each. The hydrogens α and β to the ketone carbonyl (attached to the oxirane ring), are displayed at δ 3.41 (d, J = 4 Hz) and 3.21 (d, J = 4 Hz), respectively. Four methyl singlets are observed at δ 3.70 (ester), 1.70 (vinylic), 1.30 and 0.94 (*gem*-dimethyl). The ^{13}C nmr DEPT spectrum displays two carbonyl singlets at δ 203.1 (ketone) and 171.9

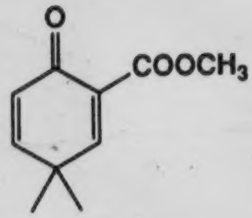
(ester), while a singlet at δ 131.8 and a doublet at δ 120.2 confirm the presence of a trisubstituted olefin in compound **57**. The carbons attached to the oxygen at the oxirane ring are displayed as doublets at δ 65.3 and 55.3. High resolution mass spectrometry gave a molecular ion signal at m/z 264.1364 consistent with the molecular formula $C_{15}H_{20}O_4$. This reaction gave a single compound, but the stereochemistry of its epoxide ring could not be determined with the data provided by nmr. Nevertheless it is expected that the approach of the nucleophilic peroxide would be from the less hindered side of the molecule. As a result, the epoxide would be *trans* to the carbomethoxy group.

Epoxides are very useful intermediates for the conversion of olefins into carbonyl compounds by treatment with mineral acid or boron trifluoride etherate.[70] Often the conversion of the epoxide to the carbonyl group is accompanied by rearrangement which may become the predominant reaction. This side reaction has been used to effect ring contraction of epoxycyclohexanones to cyclopentanones.[70, 71] Epoxidation of an α,β-unsaturated cyclohexenone furnishes an epoxide which can undergo rearrangement in the presence of boron trifluoride etherate. The product of this rearrangement is a cyclic β-keto aldehyde which may be converted to the cyclopentanone upon treatment with hydroxide.

Epoxyketone **57** was treated with boron trifluoride etherate in benzene. Unfortunately, no matter how carefully (low temperature) the reaction was run, only complete decomposition of the epoxyketone took place. Other acid treatment (trifluoroacetic acid-boron trifluoride etherate in ether) of compound **57** gave the same results.

Hydroxy lactone **43** could not be dehydrated, neither was the formation of an enol ether from ketolactone **56** possible. Therefore the formation of the double bond required for the ring cleavage could not take place. Conversion of either compound **15** or compound **14** into an α-hydroxy ketone or a 1,2-diketone was not possible. Attempted induction of the ring contraction through epoxyketone **57** did not give any positive results.

A second synthetic approach to spirodysin **43**, namely the direct formation of the 5,6-bicyclic system via a Diels-Alder reaction, required the addition of a functionalized diene to a 5-membered ring dienophile such as keto ester **53**. As little is known about the Diels-Alder cycloadditions in such systems[63] it was useful to study the addition of different dienes to compound **53**. This study was also necessary in order to decide which diene was the most appropriate for synthesis of spirodysin. As well the study of the addition of a variety of dienes to dienophile **53** under different Diels-Alder reaction conditions would provide comparative information about the Diels-Alder adducts of the cyclopentenone dienophile and cyclohexadienone dienophiles **12** and **58** previously studied in these laboratories.[14, 64]



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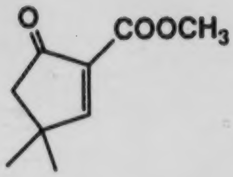
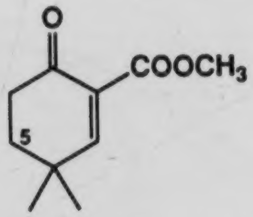
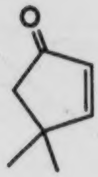


53

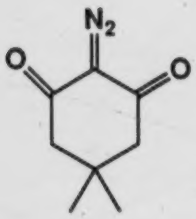


58

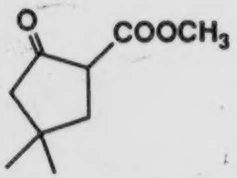
Two methods to form a cyclopentanone ring containing a *gem*-dimethyl group at a specific position are described in the literature. The first method employs an acyloin condensation on the methyl or ethyl diester of 3,3-dimethylglutaric acid.[72] The condensation is carried out with sodium in the presence of trimethylsilyl chloride. A volatile bis-silyl enol ether is produced which can be hydrolyzed to the α,β-unsaturated ketone **59** with dilute acid. In order to introduce the carbomethoxyl group present in dienophile **53** it will be necessary to reduce the double bond, carbomethoxylate the molecule and regenerate the double bond.



59



60

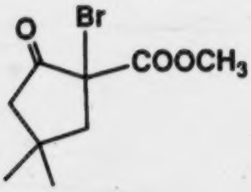


61

Compound **53** can also be prepared[73] through a Wolff rearrangement of the diazodiketone **60** in methanol, followed by an oxidation at the α-position. Obviously the latter procedure is the method of choice, since it produces the β-keto ester directly from commercially available starting materials, and acyloin condensations are known to give low to medium yields during the formation of 5-membered cyclic systems.

The diazo compound **60** could be prepared[74] from the reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with tosyl azide. Thus, dimedone[74] was treated with sodium methoxide (1 eq), followed by the addition of an ether solution of *p*-toluenesulfonyl azide to give diazodiketone **60** as yellow needles. Irradiation[73] of the diazo compound **60** in dry tetrahydrofuran with a 450 W tungsten lamp and a pyrex filter, induced a Wolff rearrangement. The intermediate ketene produced immediately reacted with the methanol (3 eq) present in the reaction mixture to give 2-carbomethoxy-4,4-dimethylcyclopentanone (**61**). Compound **61** is set up to oxidize the α-position to form the double bond, thereby furnishing keto ester **53**.

Earlier in this work, a double bond in keto ester **12** was formed either by the elimination of a bromide or through the oxidation and elimination of a selenide derivative. The difference between these two methods was made during the purification of the final keto ester **12**, which was performed in a more efficient manner when the bromide was used. Thus, the bromide method was attempted to form the double bond in the 5-membered ring keto ester **62**.



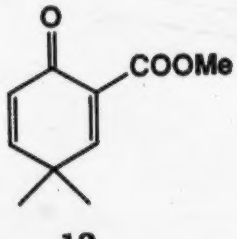
62

Bromination of keto ester **61** with *N*-bromosuccinimide in carbon tetrachloride in the dark gave bromide **62** in 93 % yield. The infrared spectrum of compound **62** displays two strong carbonyl absorptions at 1761 (ester) and 1723 cm^{-1} (ketone). The ^1H nmr spectrum displays the C-5 methylenic hydrogens as an AB system at δ 2.89 (d, $J = 15$ Hz) and 2.40 (d, $J = 15$ Hz), while the other methylenic hydrogens (C-3) are displayed together at δ 2.39. Three methyl singlets appear at δ 3.80 (ester), 1.28 and 1.10 (*gem*-dimethyl). The ^{13}C nmr APT spectrum displays carbonyl signals at δ 206.2 (ketone) and 168.3 (ester). High resolution mass spectrometry provided molecular ions with signals at m/z 250.0026 and m/z 248.0027 with almost the same intensity, consistent with the molecular formula $C_9H_{13}O_3Br$.

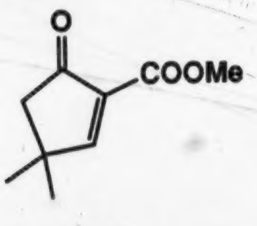
Dehydrobromination of compound **62** with 1,8-diazabicyclo[5.4.0]undec-7-ene did not produce the desired keto ester **53**. When LiCl in dimethylformamide[75] was used at room temperature a 20 % yield of keto ester **53** was obtained after bulb-to-bulb distillation. A thick residue was also produced. Compound **62** appeared sluggish in the elimination reaction to form keto ester **53**. Perhaps the more acidic α'-hydrogens of the ketone group of the cyclopentanone ring are abstracted faster than the β-hydrogen, inducing a rearrangement of the bromine from the highly hindered quaternary center to a carbon which is less sterically demanding. Since dehydrohalogenation failed to produce the olefin the selenium method was used.

Keto ester **61** was reacted with phenylselenenyl chloride in the presence of pyridine[11, 12, 64] in a dichloromethane solution at 0°C. After 45 min water was added and the organic layer was washed with 5 % aqueous hydrochloric acid and water until no pyridine was left. Hydrogen peroxide was added to the organic layer at 0°C to give a 95 % yield of dienophile **53**. The infrared spectrum of compound **53** shows strong carbonyl absorptions at 1754 (ester) and 1724 cm^{-1} (ketone) and a medium absorption at 1621 cm^{-1} (olefin). The ^1H nmr spectrum displays only four singlets: δ 8.07 (vinylic hydrogen), 3.74 (ester), 2.34 (C-5 hydrogens) and 1.20 (*gem*-dimethyl). The ^{13}C nmr APT spectrum displays carbonyl signals at δ 202.2 (ketone) and 162.2 (ester), as well as signals for a trisubstituted double bond at δ 180.2 and 133.7. High resolution mass spectrometry gave a molecular ion peak at m/z 168.0987, consistent with the molecular formula $C_9H_{12}O_3$. Elemental analysis counted for: C, 64.15 %; H, 6.96 % (calcd. for $C_9H_{12}O_3$: C, 64.25 %; H, 7.19 %).

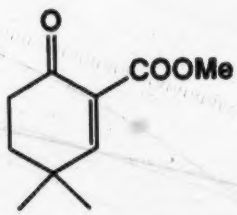
Before describing the results of the use of dienophile **53** in the Diels-Alder reaction it would be helpful to discuss the regiochemistry and stereochemistry of addition of dienes found to operate with the cyclohexadienone **12**[14] and the cyclohexenone **58**[64] systems.



12



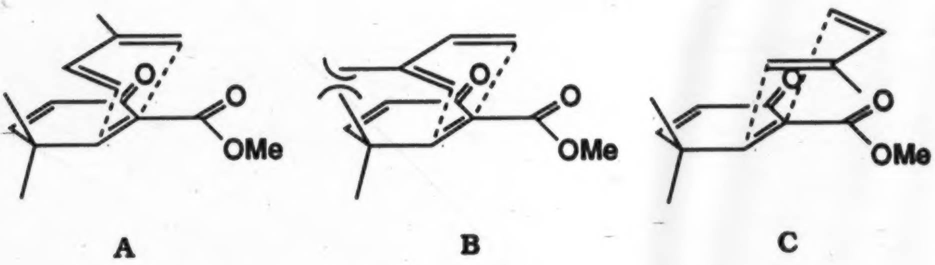
53



58

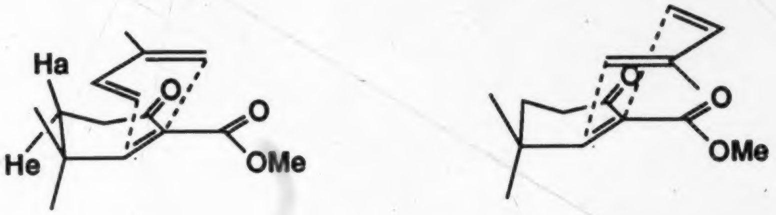
Cycloaddition of dienes to 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**12**) was found to be strongly influenced by the Lewis acid employed to catalyze the reaction. This type of cycloaddition represents the concept of "guidance by catalysis".[76, 77] During the cycloaddition reaction (Scheme 6) of isoprene to dienophile **12** there are three transition states that may be considered. In transition states **A** and **B** the diene has a secondary orbital overlap with the carbonyl of the ketone, while in transition state **C** the diene has secondary orbital overlap with the ester carbonyl. In accordance with the established "*para*" rule for the Diels-Alder reaction, transition state **B** (*endo* to the ketone) was favored if the ketone carbonyl was activated by a Lewis acid. Conversely, transition state **C** was favored if the ester carbonyl was the one that was activated. Each of these transition states would furnish a *para*-adduct.

Scheme 6



Browne[2] observed that most Lewis acids catalyzed the cycloaddition of isoprene to cyclohexadienone **12** to produce predominantly compound **13** (e.g. $SnCl_4$, 4 : 1), the *para*-adduct-*endo*-to-the-ester. However when $BF_3{\bullet}OEt_2$ was used to catalyze the Diels-Alder reaction the predominant product (7 : 3) was compound **14**, the *anti*-*para*-adduct-*endo*-to-the-ketone. These results confirm the selectivity induced by the difference in complexation of the Lewis acids with the different carbonyls in the dienophile. What was interesting during this Diels-Alder reaction with $BF_3{\bullet}OEt_2$ was the production of the *anti-para*-adduct as the major isomer. Formation of this isomer suggested that the reaction did not go through the transition state **B** but instead it reacted through the transition state **A**. The only explanation of this phenomenon was that the steric interaction between the *gem*-dimethyl group of the dienophile and the vinylic methyl group of the diene overcomes the stereoelectronic guidance of the reaction and induces the system to undertake transition state **A**. It is possible that the double bond at the other end of the molecule, opposite to the ester group, affected the stereochemical outcome of the reaction by keeping the dienophile practically flat and allowing the diene to approach the system with minor steric interactions between the two counterparts. Also an additional double bond in the molecule helped to stabilize the *endo-anti-para* transition state **A** through a secondary orbital interaction with the diene system. That this was the case was confirmed when a system such as the cyclohexenone ester **58**[64] was subjected to Diels-Alder cycloaddition with isoprene. The *para*-adduct was obtained exclusively without any effect on the regiochemistry by the Lewis acids used ($FeCl_3$, $SnCl_4$ or $BF_3{\bullet}OEt_2$). This result indicated that the remote cross conjugated double bond of cyclohexadienone **12** plays a significant role in the regiochemical outcome of the reaction, mainly because of the ability of the double bond to have secondary orbital overlap with the diene, as well as maintaining the molecule flat, reducing the steric interaction between the quasi-axial hydrogen at the C-5 methylene and the diene (Scheme 7). Therefore, it is clear that a transition state such as **D** is of higher energy and that the diene will prefer to undergo cyclization through a transition state **E**, *endo*-to-the-ester group, once the double bond has been reduced in dienone **12**.

Scheme 7



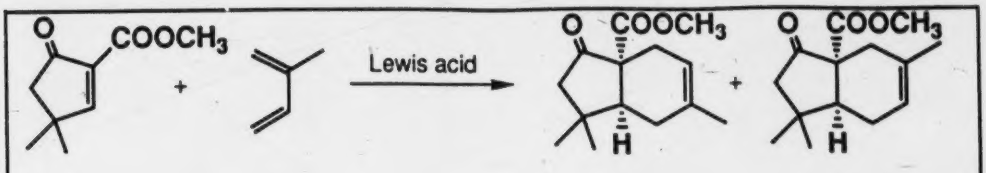
D

E

These results stimulated our interest to compare the Diels-Alder dienophiles previously studied with a similar but smaller cyclic dienophile such as dienophile **53**.

Certain Lewis acids ($SnCl_4$, $FeCl_3$, etc.), are known to form bidentate complexes with β-keto esters,[78] activating the enone from both carbonyls and increasing the *endo*-selectivity during cycloaddition. This selectivity can either be to the ketone or to the ester carbonyl. In the case of isoprene the presence of the *gem*-dimethyl group in the dienophile hinders the *para-endo*-to-the-ketone approach, favoring the *para-endo*-to-the-ester transition state (**G**). The strong Lewis acid boron trifluoride does not form a bidentate complex. Rather it coordinates preferentially with the ketone carbonyl, promoting an *endo*-to-the-ketone transition state (**F**), to give the *anti-para* adduct. The Diels-Alder cycloaddition of cyclopentenone ester **53** with isoprene (Table 2) gave a single adduct **63** when the catalyst used was $SnCl_4$, $FeCl_3$, $AlCl_3$ or $ZnCl_2$. The product obtained under these conditions was exclusively the *para*-adduct. On the other hand boron trifluoride gave an inseparable mixture of *para*- and *anti-para*-adducts **63** and **64** in 7 : 1 ratio. The thermal reaction carried out at 200°C in a sealed tube gave a 1 : 1 mixture of the same regioisomeric adducts **63** and **64**. The small regiochemical reversal caused by $BF_3 \bullet OEt_2$ with cyclopentenone ester **53** could serve as a proof that the steric interaction found between the H-5 quasi-axial hydrogen of dienophile **58** and the vinylic methyl of isoprene is large enough to overcome the secondary overlap between isoprene and the activated ketone carbonyl. Because compound **53** does not have this type of steric interaction (Scheme 8), the activation of the ketone carbonyl with $BF_3 \bullet OEt_2$ produces a small amount of the *anti-para* adduct **64** through the transition state **F**. The other Diels-Alder adduct **63** would result from cyclization through a transition state **G**, *para-endo*-to-the-ester.

Table 2. Lewis acid catalyzed Diels-Alder addition of isoprene to enone ester **53**.



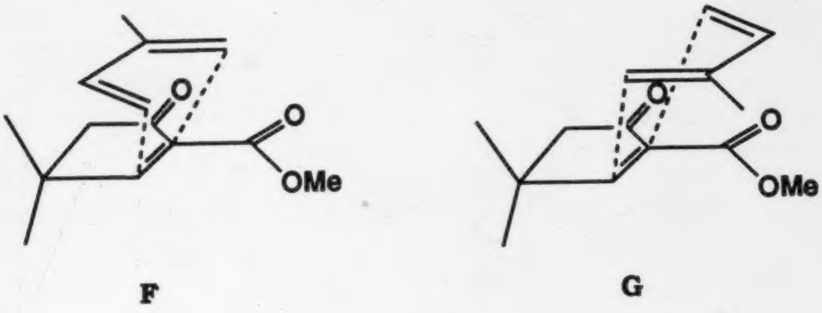
53 **63** **64**

L. Acid (eq)	Isoprene (eq)	t (h)	T (°C)	Yield (%)	Add. (ratio)
$SnCl_4$ (1)	10	10	0	86	**63**
$FeCl_3$ (1)	10	3	0	76	**63**
$AlCl_3$ (1)	10	5	0	64	**63**
$ZnCl_2$ (1.5)	10	168	0	20[a,c]	**63**
$ZnCl_2$ (1.3)	10	10	20	75	**63**
$BF_3 \bullet OEt_2$ (1)	20	150	20	89[a,d]	**63/64** (7:1)[b]
Thermal	30	11	200	>95	**63/64** (1:1)[b]

a. Based on consumed starting material.
b. Ratio calculated by nmr integrals.
c. Starting material was recovered in 38 % yield.
d. Starting material was recovered in 8 % yield.

The ether solution of the Diels-Alder reaction developed colorful solutions when Lewis acids catalysts such as $SnCl_4$ (pink-red), $FeCl_3$ (violet) or $AlCl_3$ (green) were used. Unfortunately, all these Lewis acid catalyzed reactions were accompanied with a great deal of polymerization of the diene, making the purification of the final Diels-Alder adduct rather difficult. In contrast the reaction catalyzed with $ZnCl_2$[79] or $BF_3{\bullet}OEt_2$ was clear and the purification was easy.

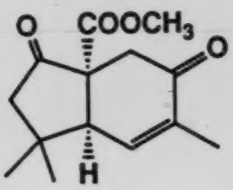
Scheme 8



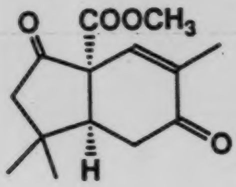
The ^1H nmr spectrum of compound **63** displays a broad signal for the vinylic hydrogen at δ 5.37 (br dd, J = 4, J' = 2.5 Hz), coupled to the signals at δ 2.86 (ddd, J = 18, J' = 4, J'' = 2 Hz) and 2.03 (ddd, J = 18, J' = 2.5, J'' = 2 Hz). The C-1 hydrogen is displayed at δ 2.79 (br d, J = 8 Hz). This signal simplified when the signals at δ 2.17 (ddd, J = 18, J' = 8, J'' = 2 Hz, C-2H) and 1.93 (br dd, J = 18, J' = 2 Hz, C-2H) were independently irradiated with a decoupler pulse. The four methyl groups appear at δ 3.71 (ester), 1.69 (vinylic), 1.20 and 0.88 (*gem*-dimethyl). The infrared spectrum of compound **63** displays two strong absorptions at 1752 (ester) and 1731 cm^{-1} (ketone). The ^{13}C nmr APT spectrum shows two carbonyl signals at δ 214.3 (ketone) and 172.5 (ester), as well as signals for a trisubstituted double bond at δ 132.6 (C-3) and 117.3 (C-4). The high resolution mass spectrum gave a molecular ion peak at m/z 236.1413 consistent with a molecular formula $C_{14}H_{20}O_3$. The *anti-para*-adduct **64** could not be separated from the *para*-adduct. However the ^{1}H nmr spectrum of the mixture shows signals that were not present in the spectrum of compound **63** at δ 5.41 (br s, 1 H, vinylic), 3.68 (s, 3 H, ester methyl), 2.71 (br s, 1 H), 2.67 (d, $J = 6$ Hz, 1 H), 2.37 (s, 2 H, -C**H**$_2$CO-), 2.21 (m, 2 H), 1.93 (d, $J = 18$ Hz, 1 H), 1.69 (s, 3H, vinylic methyl), 1.18 and 0.88 (*gem*-dimethyl). Because the minor isomer **64** could not be purified an attempt to assign its nmr signals was made by assuming a close correlation between the position of the nmr signals in both isomeric compounds **63** and **64** (based on the correlation of the nmr signals for the 6-membered isomers **13** and **14**).[14]

The regiochemistry of the addition of isoprene to dienophile **53** was assigned based on the signals in the ^{1}H nmr spectrum, together with decoupling experiments. The assignment was confirmed by the chemical derivatization of the *para*-adduct **63** to keto enone **65**. Photooxygenation[80] of the double bond of compound **63** in the presence of acetic anhydride-pyridine gave the enone **65** in 41 % yield. The ^{1}H nmr spectrum of compound **65** displays the β-hydrogen of the enone at δ 6.58 (dd, $J = 5$, $J' = 2$ Hz), the bridgehead hydrogen (H-6) at 3.31 (dd, $J = 5$, $J' = 1.5$ Hz), the vinylic methyl at δ 1.85 (dd, $J = 2$, $J' = 1.5$ Hz) and the two methylenic groups at δ 3.14 (d, $J = 17$ Hz), 2.69 (d, $J = 17$ Hz), 2.46 (d, $J = 11$ Hz) and 2.42 (d, $J = 11$ Hz). Three methyl singlets are observed at δ 3.72

(ester), 1.40 and 1.05 (*gem*-dimethyl). The ^{13}C nmr APT spectrum displays three carbonyl signals at δ 211.0, 194.4 and 171.8 and two olefinic signals at δ 139.1 and 136.3. The infrared spectrum of compound **65** displays three strong carbonyl absorptions at 1753 (ester), 1732 (ketone) and 1679 cm^{-1} (enone). High resolution mass spectrometry gave a molecular ion peak at m/z 250.1204 consistent with the molecular formula $C_{14}H_{18}O_4$.



65



80

The multiplicity of the signal for the β-hydrogen of the enone in compound **80** (δ 6.69, dd, $J = J' = 1$ Hz, *vide infra*) and the one for the enone **65** (δ 6.58, dd, $J = 5$, $J' = 2$ Hz) was sufficient evidence for the assignment of the mode of addition of isoprene to the dienophile **53**. Further evidence was provided by the multiplicity of the signal of the bridgehead hydrogen. In compound **80** H-1 resonates at δ 3.17 (ddd, $J = J' = 5$, $J'' = 1$ Hz) while in compound **65** H-6 is observed at δ 3.31 (dd, $J = 5$, $J' = 1.5$ Hz), indicating that the C-1 hydrogen of compound **80** has more vicinal hydrogens than the corresponding hydrogen in compound **65**. The chemical shift of the corresponding signal in the latter compound **65** indicated that it was an allylic hydrogen in addition to being in a bridgehead position, while the corresponding hydrogen in compound **80** was only in a bridgehead position.

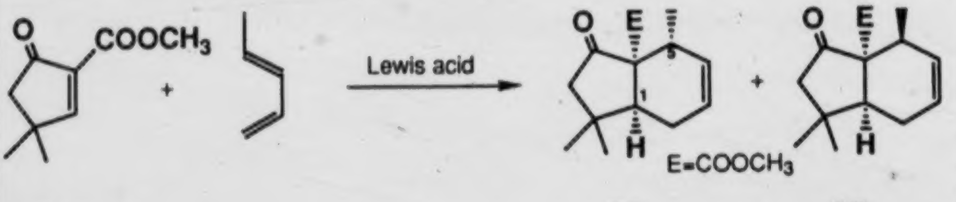
The Diels-Alder cycloaddition of dienophile **53** with *trans*-piperylene (Table 3) was performed in the presence of different Lewis acids giving, in almost all the cases studied, mixtures of two epimeric products. The reaction catalyzed by boron trifluoride was the exception. Only one epimer (**66**) was obtained in 73 % yield.

The ^{1}H nmr spectrum of the major epimer **66** displays signals for the vinylic hydrogens at δ 6.01 (ddd, J = 10, J' = 6.5, J'' = 2.5 Hz, C-3) and 5.65 (ddd, J = 10, J' = 7, J'' = 3 Hz, C-4). The hydrogen at C-5 appears at δ 2.85 as a complex multiplet. The hydrogen at C-1 is displayed at δ 2.67 (dd, J = 7, J' = 2.5 Hz) indicating that there are two hydrogens on the adjacent carbon and confirming that the regiochemistry of the Diels-Alder addition is as proposed. The signal for the methyl group of the B-ring appears at δ 1.18 (d, J = 7 Hz), while the signals for other methyl groups are displayed at δ 3.75 (ester), 1.09 and 1.07 (*gem*-dimethyl). The infrared spectrum of compound **66** shows two strong absorptions at 1742 (ester) and 1729 cm^{-1} (ketone). The ^{13}C nmr DEPT spectrum displays two singlets for the carbonyls at δ 213.2 (ketone) and 173.8 (ester). The vinylic carbons are displayed as doublets at δ 134.2 and 128.3. High resolution mass spectrometry gave a molecular ion peak for the mixture of epimers at m/z 236.1413 consistent with the molecular formula $C_{14}H_{20}O_3$. The infrared spectrum of the minor epimer **67** displays two carbonyl absorptions at 1754 (ester) and 1732 cm^{-1} (ketone). The ^1H nmr spectrum shows the signals for the vinylic hydrogens at δ 5.80 (ddd, J = 10, J' = J'' = 2.5 Hz, C-3) and 5.51 (ddd, J = 10, J' = 2.5, J'' = 2 Hz, C-4). The C-1 hydrogen could not be assigned with confidence because the signal appeared buried in a multiplet, together with the C-5 and the C-8 hydrogens. The methyl groups are displayed at δ 3.70 (ester), 1.21 (C-5, d, J = 7 Hz), 1.15 and 1.00 (*gem*-dimethyl).

The regiochemistry of the cycloaddition of *trans*-piperylene to keto ester **53** was assigned on the basis of the *ortho*-rule and via decoupling experiments. The stereochemistry of the methyl group at C-5 was assigned based on nOe experiments on both epimers. Compound **66** showed an enhancement of the signals at δ 3.75 (ester methyl, 11 %) and 2.67 (C-1 H, 6 %) upon irradiation at δ 1.18 (C-5 methyl). Irradiation at δ 2.67 (C-1 H) enhanced the signals at δ 1.18 (C-5 methyl, 11 %) and 3.75 (ester methyl, 8 %), while irradiation at δ 2.85 (C-5 H) produced an enhancement at δ 3.75 (ester methyl, 8 %). Irradiation of the minor isomer compound **67** at δ 1.21 (C-5 methyl) gave no enhancement to either the ester methyl (δ 3.70) or the C-1 H (δ 2.35). With these observations we can conclude that the stereochemistry at C-5 is as assigned. Further evidence for this assignment was provided by the relative shift of the C-5 methyl and the C-5 hydrogen of each isomer in their ^{1}H nmr spectra.[63] The ^{1}H nmr spectrum of compound **66** displays the C-5 methyl at δ 1.18 and the hydrogen at δ 2.85, while in the ^{1}H nmr spectrum of compound **67** the C-5 methyl resonates at δ 1.21 and the hydrogen at δ 2.35. Since the higher field signals should be in the shielding cone of the neighboring ester carbonyl the methyl group of compound **66** and the C-5 hydrogen of compound **67** are *cis* to the ester group, in agreement with the data obtained from the nOe experiments.

Based on the ratio of the epimeric cycloadducts **66** and **67** it was concluded that the approach of the diene to the dienophile is mainly *endo*-to-the-ester, especially for the case when boron trifluoride is used as catalyst. This observation is not consistent with other cases[2] where it has been observed that boron trifluoride activates the ketone carbonyl more than the ester carbonyl, inducing an *endo*-to-the-ketone transition state (**H**, Scheme 9). The type of steric interaction observed involving isoprene as the diene is not observed with piperylene because of the absence of the methyl group. Nevertheless, steric repulsion between the C-2 hydrogen of *trans*-piperylene and the *gem*-dimethyl group of enone ester **53** induces the diene to take the *endo*-to-the-ester transition state (**I**). It is clear now that the presence of an additional double bond in the dienophile, contributes to overcome the steric repulsion caused by the *gem*-dimethyl group.

Table 3. Lewis acid catalyzed Diels-Alder addition of *trans*-piperylene to enone ester **53**.

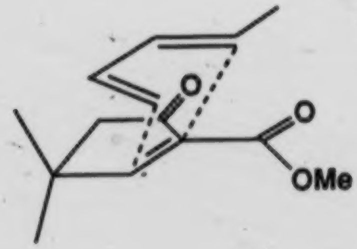

O
COOCH3
+
Lewis acid
O
E
5
1
H
+
O
E
H
E=COOCH3

53 **66** **67**

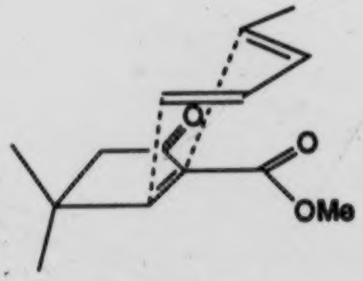
L. Acid (eq)	*trans*-Pip(eq)	t (h)	T (°C)	Yield (%)	Add. (ratio)
$SnCl_4$ (1)	10	6	0	73	**66/67**(6:1)
$FeCl_3$ (1)	10	2.5	0	50	**66/67**(2:1)
$ZnCl_2$ (1.2)	10	5	20	47[a,b]	**66/67**(1.5:1)
BF_3•OEt_2 (1)	10	90	20	73	**66**
Thermal	20	6	200	90	**66/67**(3:1)

a. Starting material was recovered in 34 % yield.
b. Based on consumed starting material.

Scheme 9



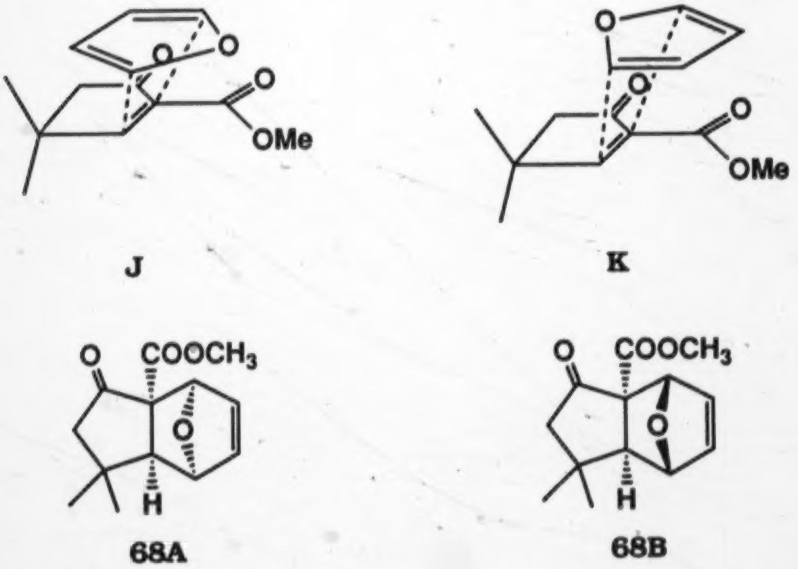
H



I

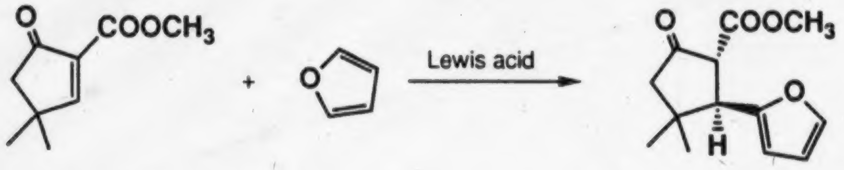
The Diels-Alder reaction of enone-ester **53** with furan should provide further proof for the mode of addition of dienes to this dienophile. If the preferred transition state is *endo*-to-the-ketone (**J**, Scheme 10), then compound **68A** would be produced. If the *endo*-to-the-ester transition state (**K**) is preferred then compound **68B** would be formed.

Scheme 10



Under the reaction conditions employed (Table 4) only the 1,4-addition product **69** was isolated. Compound **68** was not produced even under thermal conditions. The ^{1}H nmr spectrum of compound **69** displays signals at δ 7.36 (d, $J = 2$ Hz), 6.32 (dd, $J = 3$, $J' = 2$ Hz) and 6.14 (d, $J = 3$ Hz) corresponding to the furan moiety. An AX system is displayed at δ 3.78 (d, $J = 12$ Hz) and 3.69 (d, $J = 12$ Hz) which was assigned to the hydrogens at the α-carbon and at the β-carbon respectively. Methyl singlets appear at δ 3.73 (ester), 1.30 and 0.80 (*gem*-dimethyl). The infrared spectrum displays strong absorptions at 1758 (ester) and 1730 cm^{-1} (ketone) as well as a medium band at 738 cm^{-1} (furan). The ^{13}C nmr DEPT spectrum shows two carbonyl singlets at δ 208.8 (ketone) and 168.8 (ester). Signals for four aromatic carbons are also displayed at δ 151.9 (singlet), 142.0 (doublet), 110.2 (doublet) and 107.4 (doublet) which were assigned to the furan carbons. High resolution mass spectrometry gave a molecular ion peak at m/z 236.1044 consistent with the molecular formula $C_{13}H_{16}O_4$. The stereochemistry at C-2 and C-3 could not be unambiguously assigned based on the spectral data. The tentative assignment was made assuming that the facile epimerization of the β-ketoester system would allow for the exclusive formation of the more stable *trans* isomer.

Table 4. Lewis acid catalyzed Diels-Alder addition of furan to enone ester **53**.



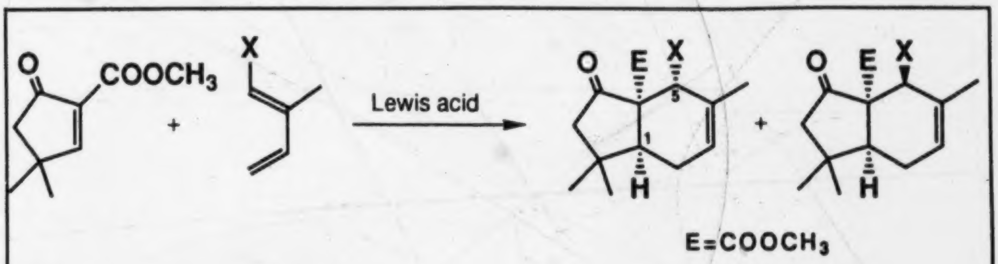
53 **69**

L. Acid (eq)	Furan (eq)	t (h)	T (°C)	Yield (%)
$SnCl_4$ (1)	10	2.5	-10	a
$FeCl_3$ (1)	10	25	0	42
$ZnCl_2$ (1)	10	48	20	b
$BF_3{\bullet}OEt_2$ (1)	10	28	20	54
Thermal	20	7	150	7[c]

a. Decomposition took place.
b. Starting material was recovered in 100 % yield.
c. Starting material was recovered in 71 % yield.

A study of the Diels-Alder cycloaddition of functionalized dienes to keto ester **53** was undertaken to determine which dienes would be suitable for the synthesis of spirodysin **46**. The C-1 functionalized diene **72A** was prepared[81] from the condensation of *trans*-2-methyl-2-butenal (tiglic aldehyde) with trimethylsilyl chloride in the presence of zinc chloride and triethylamine. The acid-sensitive trimethylsilyloxy diene was purified by distillation on a Kugelrohr apparatus at room temperature (0.55 mm Hg). It was shown to be sensitive to a variety of Lewis acid catalysts attempted, therefore it could only be used for the thermal Diels-Alder reaction (Table 5). The *tert*-butyldimethylsilyloxy derivative was also prepared hoping that it would be stable to the presence of a Lewis acid during the reaction. This diene could not be prepared with the zinc chloride-triethylamine method, so tiglic aldehyde was deprotonated at the γ-carbon with lithium diisopropylamide and the enolate was trapped with *tert*-butyldimethylsilyl chloride.[82] The product was distilled at reduced pressure in a Kugelrohr apparatus at 40°C (2.5 mm Hg). The 1-*t*-butyldimethylsilyloxy-2-methylbuta-1,3-diene **(72B)** was slightly more stable to the acidic conditions of the Diels-Alder cycloadditions (Table 5) with zinc chloride as catalyst. A poor yield (~17 % after 160 h) of a 1 : 1 mixture of epimers which could not be completely purified was obtained. When a different Lewis acid ($SnCl_4$) was used complete decomposition of the diene took place.

Table 5. Lewis acid catalyzed Diels-Alder addition of C-1 functionalized dienes **72A** and **72B** to enone ester **53**.



53 **72A:** X=OTMS **70A** **71A**

72B: X=OTBDMS **70B** **71B**

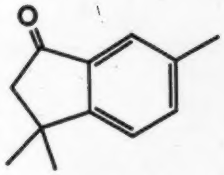
L. Acid (eq)	Diene (eq)	t (h)	T (°C)	Yield (%)	Add. (ratio)
$ZnCl_2$ (1)	**72A**(10)	16	20	-	a
$FeCl_3$ (1)	**72A**(10)	2	0	-	a
$SnCl_4$ (1)	**72A**(10)	28	-25	-	a
Thermal	**72A**(15)	12	150	86	**70A/71A**(1:1)
$ZnCl_2$ (1)	**72B**(2)	168	20	17	**70B/71B**(1:1)[b]
$SnCl_4$ (1)	**72B**(2)	5	-10	-	c

a. Decomposition took place.
b. Starting material was recovered in 52 % yield. Ratio was determined by nmr.
c. Starting material was recovered in 48 % yield.

The acid catalyzed Diels-Alder reaction with diene **72A** did not give any Diels-Alder adduct when $ZnCl_2$, $FeCl_3$ or $SnCl_4$ were used as indicated by monitoring the reactions with thin layer chromatography (tlc). When the tlc plate was developed only a large spot appeared which covered from the bottom to the top of the plate. The ^1H nmr spectrum of the crude product indicated that the diene had decomposed (polymerized?) and that the starting material had been consumed. Only the thermal reaction, carried out in a thick-walled sealed tube, gave a mixture of epimers which could be separated by flash chromatography on silica gel. The epimer **71A** that was eluted first, displays in its ^{1}H nmr spectrum a vinylic signal for the C-3 hydrogen at δ 5.66 (ddd, $J = 6$, $J' = 4$, $J'' = 2$ Hz) and an allylic signal for the C-5 hydrogen at δ 4.72 as a singlet. The C-1 hydrogen is displayed at δ 2.70 (dd, $J = J' = 8$ Hz). The multiplicity of this latter signal (dd) combined with the multiplicity of the C-5 hydrogen (s) helped to confirm the regiochemistry of the Diels-Alder cycloaddition. Several singlets appear in the spectrum for the methyl groups at δ 3.68 (ester), 1.79 (vinylic), 1.39 and 1.20 (*gem*-dimethyl) and 0.18 (9H, -OTMS). The ^{13}C nmr APT spectrum of compound **71A** shows two carbonyl signals at δ 211.9 (ketone) and 171.7 (ester), together with signals for a trisubstituted double bond at δ 136.7 (C-4) and 125.4 (C-3). The infrared spectrum displays strong absorptions at 1753 (ester) and 1726 cm^{-1} (ketone) and a medium absorption at 1251 cm^{-1} (Si-O). High resolution mass spectrometry gave a molecular ion peak at m/z 324.1750 consistent with the molecular formula $C_{17}H_{28}O_4Si$. The second compound eluted from the column was epimer **70A**. The ^{1}H nmr spectrum shows the vinylic hydrogen at δ 5.67 (ddd, $J = 6$, $J' = 4$, $J'' = 2$ Hz), the C-5 hydrogen at δ 4.40 (singlet), and the C-1 hydrogen at 2.83 (dd, $J = 8$, $J' = 4$ Hz). Singlets for the methyl groups are displayed at δ 3.68 (ester), 1.70 (vinylic), 1.05 and

0.93 (*gem*-dimethyl) and 0.08 (9H, -OTMS). The ^{13}C nmr DEPT experiment of compound **70A** gives two singlets for the carbonyls at δ 212.1 and 170.1, a singlet at δ 136.7 for the quaternary carbon (C-4) at the double bond and a doublet for the vinylic carbon (C-3) at δ 124.8. The infrared spectrum of compound **70A** displays strong carbonyl signals at 1757 (ester) and 1734 cm^{-1} (ketone) as well as a medium signal at 1250 cm^{-1} (Si-O). High resolution mass spectrometry gave a molecular ion peak at m/z 324.1753 consistent with the molecular formula $C_{17}H_{28}O_4Si$.

The stereochemistry at the C-5 carbon was assigned by a simple nOe experiment in which the C-1 or C-5 hydrogens were irradiated. Irradiation at δ 2.70 (C-1) of compound **71A** gave a 2 % enhancement of the C-5 hydrogen signal (δ 4.72). In contrast, irradiation at δ 4.72 produced an enhancement at δ 3.68 (4 %, ester methyl) and at δ 2.70 (2 %, C-1 H). On the other hand, irradiation at δ 4.40 (C-5) ~~of~~ compound **70A** produced no appreciable enhancement at δ 2.83 (C-1 H). With this data the stereochemistry at C-5 in compound **70A** was assigned as **R** (having the OTMS group *cis* to the carbomethoxyl group), while compound **71A** should have **S** configuration at C-5 (with the OTMS group *trans* to the carbomethoxyl moiety).

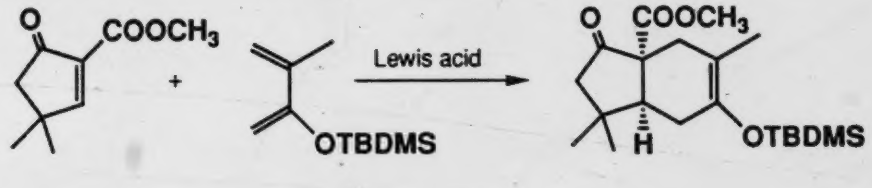


76

The regiochemistry of the Diels-Alder reaction was confirmed when independent decarbomethoxylations were performed on the epimers **70A** and **71A** using hydrated lithium iodide in refluxing collidine.[83] The same aromatic compound **76** was obtained in *ca.* 54 % yield in each case. The infrared spectrum of the aromatic ketone **76** displays absorptions at 1736 (ketone) and 825 cm^{-1} (aromatic). The ^{1}H nmr displays signals for an aromatic system at δ 7.50 (br s), 7.44 (dd, *J* = 8, *J'* = 1 Hz) and 7.38 (d, *J* = 8 Hz), as well as three singlets at δ 2.60 (2 H, C-2 H's), 2.40 (3 H, aromatic methyl) and 1.40 (6 H, *gem*-dimethyl). The high resolution mass spectrometer gave a molecular ion peak at m/z 174.1043 consistent with the molecular formula $C_{12}H_{14}O$. It seems that after decarbomethoxylation the incipient enolate eliminates the trimethylsilyloxy group from the B-ring, forming a cyclohexadiene moiety. Oxidation to furnish the aromatic system may be induced by oxygen present in the reaction solvent. The adducts **70B** and **71B** could not be purified, nevertheless the ratio was obtained from the ^{1}H nmr spectrum of the crude mixture.

The Diels-Alder reaction of diene **73** functionalized at the 2-position gave only adduct **74**. Diene **73** was prepared[81] from 2-methyl-3-buten-2-one by deprotonation at the α'-position with lithium diisopropylamide and trapping of the enolate produced with *tert*-butyldimethylsilyl chloride. The diene was obtained in ~80 % yield after distillation using a Kugelrohr apparatus at 90°C (15 mm Hg).

Table 6. Lewis acid catalyzed Diels-Alder addition of C-2 functionalized diene **73** to enone ester **53**.



53 **73** **74**

L. Acid (eq)	**73** (eq)	t (h)	T (°C)	Yield (%)	Adduct
$ZnCl_2$ (1)	2.5	49	20	93	**74**
$SnCl_4$ (1)	1.1	9	-10	37	**74**[a]
Thermal	7	12	150	77	**74**

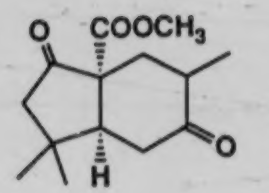
a. Obtained as the ketone **75**.

The Diels-Alder reaction of diene **73** with keto ester **53** proceeded very cleanly when zinc chloride was used, giving a better yield than that from the thermal reaction. When $SnCl_4$ was used as the catalyst a messy reaction took place and none of the adduct **74** or the starting material was recovered. Instead the hydrolyzed ketone **75** was collected in low yield and the purification of the ketone was difficult.

The ^{1}H nmr spectrum of compound **74** displays the H-1 proton signal at δ 2.87 (d, J = 8.5 Hz). This signal is slightly broad, indicating a very small (<0.5 Hz) coupling to the other vicinal hydrogen. The C-5 methylene group is displayed at δ 2.76 (dd, J = 16.5, J' = 1.5 Hz) and 2.11 (d, J = 16.5 Hz), the C-2 methylene group appears at δ 2.26 (ddd, J = 18, J' = 8.5, J'' = 1.5 Hz) and 2.03 (d, J = 18 Hz), and the C-8 methylene group is shown at δ 2.41 (d, J = 18 Hz) and 2.34 (d, J = 18 Hz). Methyl singlets are observed at δ 3.70 (ester), 1.60 (vinylic), 1.20 (*gem*-dimethyl, 3 H), 0.90 (*gem*-dimethyl and $-SiC(CH_3)_3$, 12 H) and 0.20 ($-Si(CH_3)_2$, 6 H). The infrared spectrum of compound **74** displays two strong carbonyl absortions at 1753 (ester) and 1732 cm^{-1} (ketone). Its ^{13}C nmr APT spectrum shows two carbonyl signals at δ 213.5 (ketone) and 172.1 (ester). The presence of an enol double bond is evident from carbon signals at δ 141.8 and 107.9. High resolution mass spectrometry gave a molecular ion peak at m/z 366.2227 consistent with the molecular formula $C_{20}H_{34}O_4Si$.

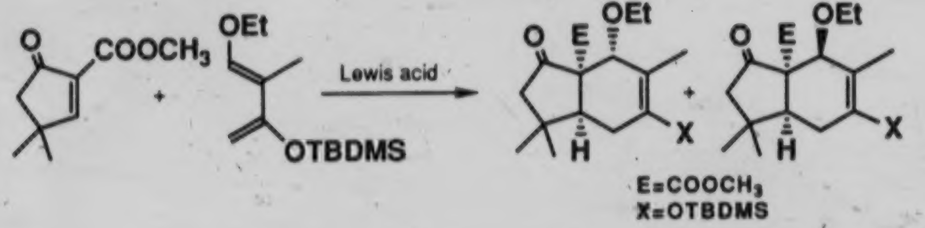
Hydrolysis of silyl enol ether **74** with diluted hydrochloric acid solution gave ketone **75** as a mixture (3.8 : 1) of epimers at C-4. The infrared spectrum of the mixture of ketones **75** shows carbonyl absorptions at 1751 (esters) and 1716 cm^{-1} (broad, ketones). The ^1H nmr spectrum displays a complex set of doubled signals which did not allowed for an unambiguous assignment. The ^{13}C nmr APT spectrum displays six carbonyl signals at δ 212.8, 211.9, 211.5, 211.2 (ketones) and 172.2 and 171.5 (esters). High resolution mass spectrometry of the mixture gave a molecular ion peak at m/z 252.1359 consistent with the molecular formula $C_{14}H_{20}O_4$.

Diene **77** can be prepared[82,84] from 4-ethoxy-3-methylbut-3-en-2-one (LDA, TBDMSCl in HMPA-THF) and purified by bulb-to-bulb distillation (2.0 mm Hg, 60°C). Diels-Alder cycloaddition of dienophile **53** with diene **77** proceeded smoothly when $ZnCl_2$ or thermal conditions were used, but when a stronger Lewis acid such as $SnCl_4$ was used as catalyst the expected Diels-Alder adduct could not be isolated from the messy reaction. Instead, the hydrolyzed ketone **80** was obtained in 36 % yield. This proved again the high acid sensitivity of this type of diene, making the Diels-Alder reactions with them somewhat limited. Nevertheless use of the less acidic Lewis acid $ZnCl_2$ allowed cycloaddition to take place giving an equal mixture of silyl enol ethers **78** and **79** in good yield. The separation of the epimeric compounds was carried out with great difficulty and was done only for identification purposes since the C-5 chiral center will be destroyed upon hydrolysis of the enol ethers.



75

Table 7. Lewis acid catalyzed Diels-Alder addition of C-1 and C-3 functionalized diene **77** to enone ester **53**.



53 **77** **78** **79**

L. Acid (eq)	**77** (eq)	t (h)	T (°C)	Yield (%)	Add. (ratio)
$ZnCl_2$ (1)	2	2	20	90	**78**/**79**(1:1)[a,b]
$SnCl_4$ (1)	2	120	-10	-	[a,c,d]
Thermal[e]	2	30	80	97	**78**/**79**(1:1)

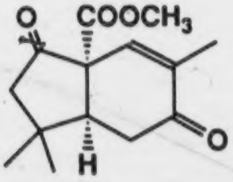
[a] Ketone **80** was obtained in (b) 9 % yield, and (c) 36 % yield.
[d] Starting material was recovered in 15 % yield.
[e] Benzene was used as solvent.

Compound **78** was the first epimer to be eluted from the column, and its infrared spectrum displays strong bands at 1753 (ester), 1728 (ketone), 1679 (enol) and 1253 cm^{-1} (Si-CH_3). The ^{1}H nmr spectrum of compound **78** displays the C-5 hydrogen at δ 4.49 (broad singlet). Interestingly, the methylenic hydrogens at the ethoxy chain appear as two sets of peaks at δ 3.46 (q, J = 7 Hz) and 3.35 (q, J = 7 Hz), suggesting that one of the diastereomeric hydrogens is affected more by the ester carbonyl than the epimeric hydrogen. The methyl group is displayed at δ 1.05 (dd, $J = J' = 7$ Hz). The C-1 hydrogen appeared at δ 2.91 (dd, $J = J' = 8$ Hz) at higher field with respect to the corresponding hydrogen in the epimeric compound (δ 3.16). The vinylic methyl group appears at δ 1.71 as a doublet ($J = 1.5$ Hz). Six singlets are observed for the methyls at δ 3.65 (ester), 0.96 (9 H, -Si-*t*-butyl), 0.90 and 0.86 (*gem*-dimethyl), 0.12 and 0.11 (-Si-methyls). The ^{13}C nmr APT spectrum shows two carbonyl absorptions at δ 211.1 (ketone) and 171.1 (ester) together with two disubstituted olefinic carbons at δ 149.0 and 112.2. High resolution mass spectrometry on the mixture of epimers failed to provide a molecular ion peak. Therefore chemical ionization was used to confirm the molecular weight of 411, consistent with the molecular formula $C_{22}H_{38}O_5Si$.

The infrared spectrum of the second epimer to be eluted (**79**) displays strong absorptions at 1755 (ester), 1732 (ketone), 1679 (enol) and 1229 cm^{-1} (Si-CH_3). The ^1H nmr spectrum of compound **79** shows the C-5 hydrogen at δ 4.35 as a singlet. The methylenic hydrogens of the ethoxyl group are displayed together at δ 3.42 (q, $J = 7$ Hz). The methyl group of this chain appears at δ 1.09 (t, $J = 7$ Hz). The C-1 hydrogen is displayed at δ 3.16 (dd, $J = 7.5$, $J' = 1.5$ Hz) and the vinylic methyl group at δ 1.63 (d, $J = 2$ Hz). Irradiation of this signal to induce decoupling affects only the signal at δ 2.71, indicating a homo-allylic coupling with this particular hydrogen. Several singlets are observed for the methyl groups at δ 3.68 (ester), 0.98 (*gem*-dimethyl), 0.95 (12 H, *gem*-dimethyl, -Si-*t*-butyl), 0.14 and 0.13 (-Si-methyls). The ^{13}C nmr APT spectrum displays two carbonyl peaks at δ 210.2 (ketone) and 169.4 (ester), together with two signals representing tetrasubstituted olefinic carbons at δ 149.9 and 110.7.

Although a clear assignment of the stereochemistry at C-5 was not possible with the data obtained from the ^{1}H nmr spectrum, it is interesting to observe that the methylene hydrogens in the ethoxy chain appear as separate signals in the case of compound **78** at δ 3.46 (q, *J* = 7 Hz) and 3.35 (q, *J* = 7 Hz), and as one single signal in compound **79** at δ 3.42 (q, *J* = 7 Hz). If it is assumed that the proximity of one of the diastereomeric hydrogens to the ester carbonyl, would induce a larger chemical shift than in the other hydrogen in the methylene carbon, then silyl enol ether **78** would have the ethoxyl group *cis* to the ester moiety. Also the C-1 hydrogen in compound **78** is at higher field (δ 2.91) in the ^{1}H nmr spectrum than the corresponding hydrogen of the epimer **79** (δ 3.16), indicating that the C-1 hydrogen in compound **78** could be within the shielding area of the ether oxygen. This is not the case for silyl enol ether **79**. The stereochemical assignment at C-5 in purely speculative and because the center at C-5 will be destroyed in a later stage in the synthesis, the stereochemistry at this position is not of crucial importance except for providing information about the mode of addition of the diene during the

Diels-Alder reaction. But as the ratio of stereoisomers obtained was always 1 : 1 there was no stereoselectivity during the Diels-Alder cycloaddition.



80

Hydrolysis in THF of the mixture of silyl enol ethers with a 0.1*N* HCl solution gave the α,β-unsaturated ketone **80** in 70 % yield. Keto ester **80** shows strong absorptions in the infrared spectrum at 1756 (ester), 1727 (ketone) and 1679 cm^{-1} (enone). The ^{1}H nmr spectrum of compound **80** displays the β-hydrogen (C-5) of the unsaturated ketone at δ 6.69 (dd, $J = J = 1$ Hz). The C-1 hydrogen is displayed at δ 3.17 (ddd, $J = J' = 5$, $J'' = 1$ Hz) and the adjacent C-2 hydrogens appear together at δ 2.67 (d, $J = 5$ Hz). Four methyl singlets are observed in the spectrum at δ 3.77 (ester), 1.83 (vinylic), 1.24 and 0.79 (*gem*-dimethyl). The ^{13}C nmr DEPT spectrum displays three carbonyl absorptions as singlets at δ 209.0 (ketone), 196.3 (enone) and 169.5 (ester). Also a doublet (δ 138.8) and a singlet (δ 136.9) are displayed for the olefinic bond of the enone. High resolution mass spectrometry gave a molecular ion peak at m/z 250.1200 consistent with the molecular formula $C_{14}H_{18}O_4$.

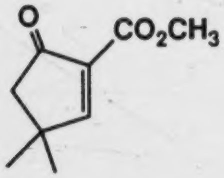
In conclusion, the Diels-Alder studies on cyclopentenone **53** are complementary to the work previously carried out in these laboratories on similar systems. Also, these studies have shown the route for the new approach to spirodysin. Compound **80** could be converted to a system which will allow for the dialkylation at the α'-position of the ketone in the cyclopentanone ring. Further studies are under way in these laboratories.

Experimental

General and Materials.

For general and materials used in Chapter 2, refer to Chapter 1 of this work.

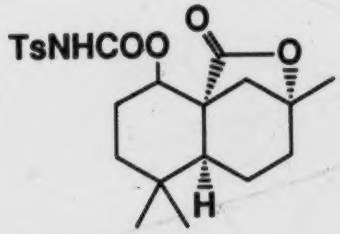
2-Carbomethoxy-4,4-dimethylcyclopent-2-en-1-one (53).



53

Phenylselenenyl chloride (7.5 g, 32 mmol) was dissolved in dichloromethane (200 mL) and the solution cooled in an ice-water bath. Dry pyridine (3.20 mL, 40 mmol) was slowly added and the solution stirred for 45 min, then 2-carbomethoxy-4,4-dimethylcyclopentan-1-one (**61**)(5.46 g, 32 mmol) dissolved in dichloromethane (30 mL) was added to the reaction mixture. The solution was stirred at 0°C for an additional 45 min then poured into an ice-5 % HCl mixture. The organic layer was washed with 5 % HCl (3 x 10 mL) and dried ($MgSO_4$). Hydrogen peroxide (30 %, 6 mL) was added to the dichloromethane solution at 0°C and allowed to react for 10 min. Additional hydrogen peroxide (30 %, 6 mL) was then added. After another 10 min, the reaction was quenched with water (20 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic extracts were combined, washed with water (2 x 5 mL), aqueous 5 % sodium bicarbonate (1 x 5 mL) and brine (1 x 5 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (0~20 % ether in petroleum ether) gave a colorless oil (3.22 g, 20 mmol, 62 %): ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H, =C**H**-), 3.74 (s, 3 H, $-OCH_3$), 2.34 (s, 2 H, -C**H**$_2$CO-) and 1.20 (s, 6 H); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 202.2 (p), 180.2 (a), 162.2 (p), 133.7 (p), 51.8 (a), 51.0 (p), 38.8 (p) and 27.3 (a); ir ($CHCl_3$ cast) 1754 (ester), 1724 (ketone) and 1621 cm^{-1} (olefin); ms M$^+$ 168.0987 (calcd. for $C_9H_{13}O_3$: 168.0987). Anal. calcd for $C_9H_{13}O_3$: C, 64.15 %; H, 6.95 %; found: C, 64.26 %; H, 7.19 %.

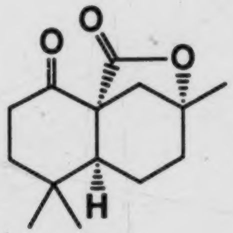
(1R*, 4S*, 9R*)-8-*p*-Toluenecarbamyl-1,5,5-trimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecan-10-one (55).



55

A catalytic amount of sodium hydride (60 % dispersion in mineral oil) was added to a benzene solution (1.0 mL) of hydroxy lactone **43** (20 mg, 0.086 mmol) and *p*-toluenesulfonyl isocyanate (24 µL, 0.25 mmol). The reaction was stirred at room temperature for 10 h then quenched with water (0.5 mL). The aqueous layer was extracted with dichloromethane (2 x 2mL) and the organic extracts were combined, washed with water (2 x 2 mL) and brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (0-10 % ether in petroleum ether) gave carbamate **55** as a colorless oil (17 mg, 0.040 mmol, 45 %): ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8 Hz, 2 H, aromatic), 7.31 (d, J = 8 Hz, 2 H, aromatic), 4.87 (br s, 1 H, ArN**H**COOCH-), 3.94 (dd, J = 12, J' = 4 Hz, 1 H, ArNHCOOC**H**-), 2.45 (s, 3 H, C**H**$_3$Ar-), 2.22 (d, J = 12 Hz, 1 H, **H**-12), 2.04 (d, J = 12 Hz, 1 H, **H**-12), 1.90-1.30 (complex, 9 H), 1.50 (s, 3 H, -C(C**H**$_3$)O-), 1.03 (s, 3 H) and 0.95 (s, 3 H, *gem*-dimethyl); ir ($CHCl_3$ cast) 3200 (N-H), 1750 (broad, carbamate, lactone), 885 and 547 cm^{-1} (aromatic); ms M^+ 238.1567 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

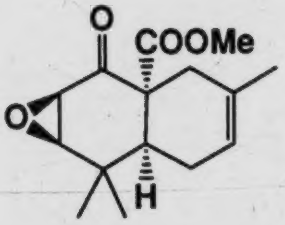
(1R*, 6S*, 9R*)-5,5,9-Trimethyl-10-oxa-tricyclo[7.2.1.0^{4,9}]-dodecan-2,11-dione (56).



56

Hydroxylactone **43** (160 mg, 0.67 mmol) was dissolved in dichloromethane. Pyridinium chlorochromate impregnated on alumina (0.9 mmol/g, 2.2 g, 2.0 mmol) was added and the slurry was stirred for 48 h. Using Florisil as filter aid the solution was filtered and the solid rinsed with dichloromethane. The filtrate was concentrated and the residual oil purified by flash chromatography on silica gel (0~30 % ether in petroleum ether) to give keto lactone **56** (155 mg, 0.65 mmol, 98 %) as a colorless oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.65 (ddd, J = 18, J' = 7, J'' = 5 Hz, 1 H, -C**H**HCO-), 2.42 (ddd, J = 18, J' = 9, J'' = 7 Hz, 1 H, -CH**H**CO-), 2.30 (dd, J = 12, J' = 2 Hz, 1 H, -CC**H**HC(CH_3)O-), 2.14 (d, J = 12 Hz, 1 H, -CCH**H**C(CH_3)O-), 2.14-2.08 (complex m, 1 H, -C(CH_3)$_2$C**H**CH$_2$-), 1.92-1.60 (complex m, 6 H, -C**H$_2$**C(CH_3)$_2$-, -OC(CH_3)C**H$_2$**CH$_2$-, -OC(CH_3)CH$_2$C**H$_2$**-), 1.50 (s, 3 H, -C(C**H$_3$**)O-), 1.05 (s, 3 H, -C**H$_3$**) and 1.00 (s, 3 H, -C**H$_3$**); ^{13}C nmr DEPT (100.6 MHz, $CDCl_3$) δ 207.8 (s), 176.0 (s), 83.7 (s), 58.8 (s), 44.0 (q), 39.7 (t), 36.6 (t), 35.5 (t), 33.3 (s), 32.6 (t), 29.7 (d), 25.1 (q), 21.1 (q) and 19.2 (t); ir ($CHCl_3$ cast) 1779 (lactone) and 1706 cm^{-1} (ketone); ms M$^+$ 236.1415 (calcd. for $C_{14}H_{20}O_3$: 236.1413). Anal. calcd. for $C_{14}H_{20}O_3$: C, 71.14; H, 8.53; found: C, 70.85; H, 8.39.

(1R*, 7S*)-1-Carbomethoxy-6,6,10-trimethyl-4-oxatricyclo-[5.4.0.0^{3,5}]undec-9-en-2-one (57)

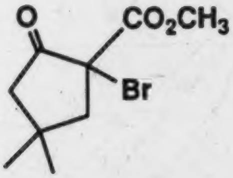


57

Pure keto ester **14** (180 mg, 0.73 mmol) was dissolved in dry benzene (30 mL). *tert*-Butyl hydroperoxide (3.0 M solution in 2,2,4-trimethylpentane, 0.7 mL, 2.1 mmol) was added followed by Triton B (benzyltrimethyl ammonium hydroxide, 40 wt. % solution in methanol, 0.2 mL, 0.44 mmol). The reaction mixture was stirred at room temperature for 24 h, then quenched by the addition of 5 mL of 10 % aqueous HCl. The aqueous layer was extracted with ether (3 x 3 mL). The organic extracts were combined and washed successively with water (2 x 3 mL) and brine (1 x 3 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography on silica gel (0-5 % ether in petroleum ether) afforded epoxy ester **57** (185 mg, 0.63 mmol, 98 %) as a colorless oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.42 (br dd, *J* = *J'* = 5 Hz, 1 H, =C**H**-), 3.70 (s, 3 H,

-OC**H**$_3$), 3.41 (d, *J* = 4 Hz, 1 H, -COC**H**OCH-), 3.21 (d, *J* = 4 Hz, 1 H, -COCHOC**H**-), 2.69 (dd, *J* = 7, *J'* = 4 Hz, 1 H, -C**H**CH$_2$CH=), 2.32 (d, *J* = 17 Hz, 1 H, -C**H**HC(CH$_3$)=), 2.16 (d, *J* = 17 Hz, 1 H, -CH**H**C(CH$_3$)=), 2.08 (ddd, *J* = 17, *J'* = 7, *J''* = 5 Hz, 1 H, -CHC**H**HCH=), 1.94 (ddd, *J* = 17, *J'* = 5, *J''* = 4 Hz, 1 H, -CHCH**H**CH=), 1.70 (s, 3 H, -C(C**H**$_3$)=CH-), 1.30 (s, 3 H, -C**H**$_3$) and 0.94 (s, 3 H, -C**H**$_3$); ^{13}C nmr DEPT (100.6 MHz, CDCl$_3$) δ 203.1 (s), 171.9 (s), 131.8 (s), 120.2 (d), 65.3 (d), 56.8 (s), 55.3 (d), 52.8 (q), 38.7 (d), 33.9 (s), 33.6 (t), 28.1 (q), 23.5 (t), 22.9 (q) and 21.1 (q); ir (CHCl$_3$ cast) 1746 (ester), 1719 (ketone) 1708 and 1225 cm^{-1} (olefin); ms M$^+$ 264.1364 (calcd. for $C_{15}H_{20}O_4$: 264.1361).

2-Bromo-2-carbomethoxy-4,4-dimethylcyclopentan-1-one (62).



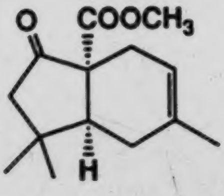
62

2-Carbomethoxy-4,4-dimethylcyclopentan-1-one (**61**) (700 mg, 4.1 mmol) was dissolved in carbon tetrachloride (10 mL). *N*-Bromosuccinimide (890 mg, 5.0 mmol) was added at once and the solution was stirred at room temperature for 10 h. The solid formed during the reaction was filtered and the filtrate was concentrated to give a yellowish oil (950 mg, 3.8 mmol, 93 %): ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.80 (s, 3 H, $-OCH_3$), 2.89 (d, *J* = 15 Hz, 1 H, -C**H**HCOCBr-), 2.40 (d, *J* = 15 Hz, 1 H, -CH**H**COCBr-), 2.39 (2 H, -COCBrC**H**$_2$-), 1.28 (s, 3 H) and 1.10 (s, 3 H); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 206.2 (a), 168.3 (a), 59.3 (a), 54.0 (p), 52.2 (a), 51.0 (a), 34.0 (a), 29.6 (p) and 29.4 (p); ir ($CHCl_3$ cast) 1761 (ester) and 1723 cm^{-1} (ketone); ms M$^+$ 250.0026 and 248.0027 (calcd. for $C_9H_{13}O_3Br$: 250.0027 and 248.0048).

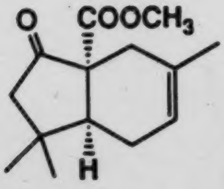
Diels-Alder reactions of keto ester 53.

The reactions were carried out using the general procedure illustrated below for isoprene. Temperature and time of reactions as well as quantities of diene and Lewis acid relative to **53** are noted in Tables 2-7. Purification and separation of the adducts were carried out using 0-10 % ether in petroleum ether as eluant. When separation occurred, the products are reported in order of elution.

(1S*, 6R*)-6-Carbomethoxy-3,9,9-trimethylbicyclo[4.3.0]non-3-en-7-one (63) and (1S*, 6R*)-6-carbomethoxy-4,9,9-trimethylbicyclo[4.3.0]non-3-en-7-one (64).



63



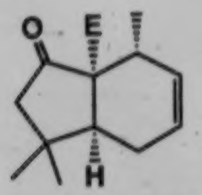
64

Lewis acid catalyzed reactions (other than zinc chloride): Keto ester **53** (25 mg, 0.15 mmol) was dissolved in dry ether (1 mL) and placed under an argon atmosphere. The reaction mixture was cooled with an ice-water bath. Tin(IV) chloride (18 µL, 0.15 mmol) was added and the reaction stirred for 15 min. Isoprene (150 µL, 1.5 mmol) was introduced into the reaction vessel by means of a syringe. The reaction was left to react for 10 h, then quenched by the addition of saturated aqueous sodium bicarbonate (1 mL). The aqueous layer was extracted with ether (3 x 1 mL). The organic extracts were combined, washed with water (2 x 2 mL) and brine (1 x 1 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (0~5 % ether in petroleum ether) gave pure compound **63** (30 mg, 86 %): ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.37 (br dd, $J = 4$, $J' = 2.5$ Hz, 1 H, $-C(CH_3)=C\mathbf{H}-$), 3.71 (s, 3 H, $-OCH_3$), 2.86 (ddd, $J = 18$, $J' = 4$, $J'' = 2$ Hz, 1 H, $-C\mathbf{H}HCH=$), 2.79 (br d, $J = 8$ Hz, 1 H, $-C(CH_3)_2C\mathbf{H}CH_2-$), 2.37 (s, 2 H, $-CH_2CO-$), 2.17 (ddd, $J = 18$, $J' = 8$, $J'' = 2$ Hz, 1 H, $-CHC\mathbf{H}HC(CH_3)=$), 2.03 (ddd, $J = 18$, $J' = 2.5$, $J'' = 2$ Hz, $-CH\mathbf{H}CH=$), 1.93 (br dd, $J = 18$, $J' = 2$ Hz, 1 H, $-CHCH\mathbf{H}C(CH_3)=$), 1.69 (s, 3 H, $-CH=C(C\mathbf{H}_3)-$), 1.20 (s, 3 H, $-C\mathbf{H}_3$) and 0.88 (s, 3 H, $-C\mathbf{H}_3$); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 214.3 (p), 172.5 (p), 132.6 (p), 117.3 (a), 57.4 (p), 53.1 (p), 52.8 (a), 47.1 (a), 37.2 (p), 30.0 (a), 27.2 (p), 25.3 (p), 23.6 (a) and 23.6 (a); ir ($CHCl_3$ cast) 1752 (ester), 1731 cm^{-1} (ketone); ms M^+ 236.1413 (calcd. for $C_{14}H_{20}O_3$: 236.1413). Anal. calcd. for $C_{14}H_{20}O_3$: C, 71.14; H, 8.53; found: C, 71.21; H, 8.49.

Zinc chloride catalyzed Diels-Alder: Zinc chloride (45 mg, 0.33 mmol) was added to dry ether (2 mL) and stirred at room temperature until all the solid had dissolved (~30 min). A solution of keto ester **53** (43 mg, 0.26 mol) in dry ether (1 mL) was added to the cloudy solution of zinc chloride followed immediately by isoprene (260 µL, 2.6 mmol). The reaction was allowed to react at room temperature for 10 h, then a saturated solution of aqueous sodium bicarbonate (1 mL) was added. The aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were washed with water (2 x 2 mL) and brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the residual oil by flash chromatography on silica gel (0~5 % ether in petroleum ether) gave adduct **63** (46 mg, 75 %).

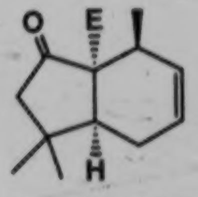
Thermal conditions: Keto ester **53** (50 mg, 0.30 mmol) was introduced into a small thick-walled ampule. Isoprene (0.90 mL, 9 mmol) was added by means of a syringe and argon was passed through the solution for 5 min. The glass container was cooled with liquid nitrogen until the solution had solidified. While the ampule was still in the nitrogen it was sealed, then allowed to warm to room temperature during 20 min. The ampule was placed in a protected oven and heated to 200°C for 10 h. The oven was turned off and the temperature allowed to reach ambient temperature. Purification by flash chromatography on silica gel (0-5 % ether in petroleum ether) gave an inseparable 1 : 1 mixture of compounds **63** and **64** (70 mg, 98 %). This mixture shows the following signals which are not present in the spectra of pure compound **63**: ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.41 (br s, 1 H, $-C(CH_3)=C\mathbf{H}-$), 3.68 (s, 3 H, $-OC\mathbf{H}_3$), 2.71 (br s, 2 H, $-C\mathbf{H}_2C(CH_3)=$), 2.67 (d, J = 6 Hz, 1 H, $-C\mathbf{H}CH_2CH=$), 2.37 (s, 2 H, $-C\mathbf{H}_2CO-$), 1.69 (s, 3 H, $-CH=C(C\mathbf{H}_3)-$), 1.18 (s, 3 H, $-C\mathbf{H}_3$) and 0.88 (s, 3 H, $-C\mathbf{H}_3$), other peaks are overlapped with those of the other isomer; ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 214.0 (p), 172.2 (p), 130.4 (p), 119.5 (a), 58.9 (p), 53.2 (p), 52.6 (a), 46.1 (a), 37.1 (p), 31.1 (p), 30.0 (a), 23.5 (a), 23.4 (a) and 21.1 (p).

(1S*, 5R*, 6R*)-6-Carbomethoxy-5,9,9-trimethylbicyclo[4.3.0]-non-3-en-7-one (66) and (1S*, 5S*, 6R*)-6-carbomethoxy-5,9,9-trimethylbicyclo[4.3.0]non-3-en-7-one (67).



E=COOCH$_3$

66



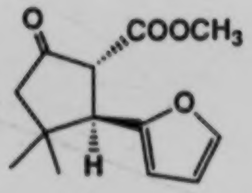
E=COOCH$_3$

67

Major isomer 66: ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.01 (ddd, J = 10, J' = 6.5, J'' = 2.5 Hz, 1 H, $-CH(CH_3)CH=C\mathbf{H}-$), 5.65 (ddd, J = 10, *J'* = 7, *J''* = 3 Hz, 1 H, -CH(CH$_3$)C**H**=CH-), 3.75 (s, 3 H, -OC**H**$_3$), 2.85 (complex m, 1 H, -C**H**(CH$_3$)CH=CH-), 2.67 (dd, *J* = 7, *J'* = 2.5 Hz, 1 H, -C(CH$_3$)$_2$C**H**CH$_2$-), 2.39 (ddd, *J* = 15, *J'* = 7, *J''* = 3 Hz, 1 H, -CHC**H**HCH=CH-), 2.10 (complex m, 3 H, -CHCH**H**CH=CH-, -C**H**$_2$CO-), 1.18 (d, *J* = 7 Hz, 3 H, -CH(C**H**$_3$)CH=CH-), 1.09 (s, 3 H, -C**H**$_3$) and 1.07 (s, 3 H, -C**H**$_3$); ^{13}C nmr DEPT (100.6 MHz, CDCl$_3$) δ 213.2 (s), 173.8 (s), 134.2 (d), 128.3 (d), 65.4 (s), 55.4 (t), 52.6 (d), 37.0 (s), 35.1 (q), 31.6 (d), 25.9 (q), 24.4 (t), 15.9 (q) and 5.8 (q); ir (CHCl$_3$ cast) 1742 (ester), 1729 cm^{-1} (ketone); ms M$^+$ 236.1413 (calcd. for $C_{14}H_{20}O_3$: 236.1413).

Minor isomer 67: ^{1}H nmr (400 MHz, CDCl$_3$) δ 5.80 (ddd, *J* = 10, *J'* = *J''* = 2.5 Hz, 1 H, -CH(CH$_3$)CH=C**H**-), 5.51 (ddd, *J* = 10, *J'* = 2.5, *J''* = 2 Hz, 1 H, -CH(CH$_3$)C**H**=CH-), 3.70 (s, 3 H, -OC**H**$_3$), 2.38 (dd, *J* = 16, *J'* = 2 Hz, 1 H, -CHC**H**HCH=CH-), 2.35 (complex, 4 H, -C**H**(CH$_3$)CH=CH-, -C(CH$_3$)$_2$C**H**CH$_2$-, -C**H**$_2$CO-), 2.06 (ddd, *J* = 16, *J'* = *J''* = 2.5 Hz, 1 H, -CHCH**H**CH=CH-), 1.21 (d, *J* = 7 Hz, 3 H, -CH(C**H**$_3$)CH=CH-), 1.15 (s, 3 H, -C**H**$_3$) and 1.00 (s, 3 H, -C**H**$_3$); ^{13}C nmr DEPT (100.6 MHz, CDCl$_3$) δ 213.6 (s), 171.5 (s), 130.0 (d), 125.2 (d), 60.2 (s), 53.4 (t), 51.8 (d), 49.2 (q), 36.8 (s), 31.7 (d), 30.1 (q), 23.8 (q), 21.4 (t) and 16.5 (q); ir (CHCl$_3$ cast) 1754 (ester) and 1732 cm^{-1} (ketone).

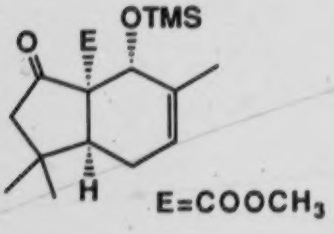
(2R*, 3R*)-3-Furyl-2-carbomethoxy-4,4-dimethylcyclopentan-1-one (69).



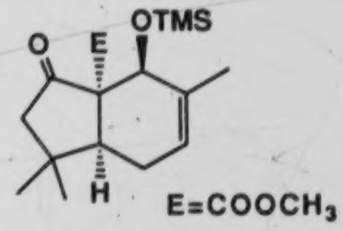
69

Furan adduct 69: ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2 Hz, 1 H, -OC**H**=CHCH=C-), 6.32 (dd, *J* = 3, *J'* = 2 Hz, 1 H, -OCH=C**H**CH=C-), 6.14 (d, *J* = 3 Hz, 1 H, -OCH=CHC**H**=C-), 3.78 (d, *J* = 12 Hz, 1 H, -COC**H**($COOCH_3$)CH-), 3.73 (s, 3 H, -OC**H**$_3$), 3.69 (d, *J* = 12 Hz, 1 H, -COCH($COOCH_3$)C**H**-), 2.40 (s, 2 H, -C**H**$_2$COCH-), 1.30 (s, 3 H, -C**H**$_3$) and 0.80 (s, 3 H, -C**H**$_3$); ^{13}C nmr DEPT (100.6 MHz, $CDCl_3$) δ 208.8 (s), 168.8 (s), 151.9 (s), 142.0 (d), 110.2 (d), 107.4 (d), 57.5 (d), 54.1 (t), 52.6 (q), 49.5 (d), 38.4 (s), 27.7 (q) and 23.4 (q); ir ($CHCl_3$ cast) 1758 (ester), 1730 cm^{-1} (ketone) and 738 cm^{-1} (furan); ms M$^+$ 236.1044 (calcd. for $C_{13}H_{16}O_4$: 236.1049).

(1S*, 5R*, 6R*)-6-Carbomethoxy-4,9,9-trimethyl-5-trimethylsilyloxybicyclo[4.3.0]non-3-en-7-one (70A) and (1S*, 5S*, 6R*)-6-carbomethoxy-4,9,9-trimethyl-5-trimethylsilyloxybicyclo[4.3.0]-non-3-en-7-one (71A).



70A

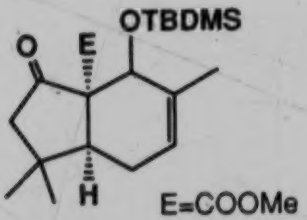


71A

Compound 70A: ^{1}H nmr (400 MHz, CDCl$_3$) δ 5.67 (dd, *J* = 6, *J'* = 5 Hz, 1 H, -CH(OTMS)C(CH$_3$)=C**H**-), 4.40 (s, 1 H, -C**H**(OTMS)C(CH$_3$)=CH-), 3.68 (s, 3 H, -OC**H**$_3$), 2.83 (dd, *J* = 7, *J'* = 4 Hz, 1 H, -C(CH$_3$)$_2$C**H**CH$_2$-), 2.50 (ddd, *J* = 16.5, *J'* = 7, *J''* = 5 Hz, 1 H, -CHC**H**HCH=C(CH$_3$)-), 2.19 (d, *J* = 17 Hz, 1 H, -C**H**HCO-), 2.08 (d, *J* = 17 Hz, 1 H, -CH**H**CO-), 2.00 (ddd, *J* = 16.5, *J'* = 6, *J''* = 4 Hz, 1 H, -CHCH**H**CH=C(CH$_3$)-), 1.70 (br s, 3 H, -CHCH$_2$CH=C(C**H**$_3$)-), 1.05 (s, 3 H, -C**H**$_3$), 0.93 (s, 3 H, -C**H**$_3$) and 0.08 (s, 9 H, -OSi(C**H**$_3$)$_3$); ^{13}C nmr DEPT (100.6 MHz, CDCl$_3$) δ 212.1 (s), 170.1 (s), 136.7 (s), 124.8 (d), 72.9 (d), 68.2 (s), 52.9 (t), 52.3 (q), 47.4 (d), 36.4 (s), 30.4 (q), 25.2 (q), 22.6 (t), 21.0 (q) and 0.25 (q); ir (CHCl$_3$ cast) 1757 (ester), 1734 (ketone) and 1250 cm^{-1} (Si-CH$_3$); ms M$^+$ 324.1753 (calcd. for $C_{17}H_{28}O_4Si$: 324.1757).

Compound 71A: ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.66 (ddd, J = 6, J' = 5, J'' = 1.5 Hz, 1 H, $-CH(OTMS)C(CH_3)=C\mathbf{H}-$), 4.72 (s, 1 H, $-C\mathbf{H}(OTMS)C(CH_3)=CH-$), 3.68 (s, 3 H, $-OC\mathbf{H}_3$), 2.70 (dd, J = J' = 8 Hz, 1 H, $-C(CH_3)_2C\mathbf{H}CH_2-$), 2.30 (d, J = 16 Hz, 1 H, $-C\mathbf{H}HCO-$), 2.35~2.25 (complex, 1 H, $-CHC\mathbf{H}HCH=C(CH_3)-$), 2.20-2.10 (multiplet, 2 H, $-CH\mathbf{H}CO-$, $-CHCH\mathbf{H}CH=C(CH_3)-$), 1.79 (d, J = 1.5 Hz, 3 H, $-CHCHHCH=C(C\mathbf{H}_3)-$), 1.39 (s, 3 H, $-C\mathbf{H}_3$), 1.20 (s, 3 H, $-C\mathbf{H}_3$) and 0.18 (s, 9 H, $-OSi(C\mathbf{H}_3)_3$); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 211.9 (p), 171.7 (p), 136.7 (p), 125.4 (a), 70.3 (a), 67.7 (p), 54.6 (p), 52.5 (a), 47.9 (a), 35.7 (p), 31.5 (a), 24.1 (a), 22.4 (p), 21.5 (a) and 0.17 (a); ir ($CHCl_3$ cast) 1753 (ester), 1726 (ketone) and 1251 cm^{-1} ($Si-CH_3$); ms M$^+$ 324.1750 (calcd. for $C_{17}H_{28}O_4Si$: 324.1757).

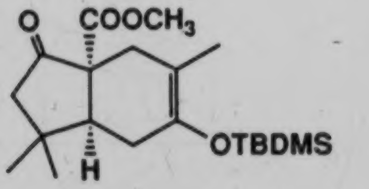
(1S*, 6R*)-6-Carbomethoxy-4,9,9-trimethyl-5-*t*-butyldimethylsilyloxybicyclo[4.3.0]non-3-en-7-one (70B and 71B).



70B and 71B

Compound 70B and 71B: ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.83 (br s, 1 H, $=C\mathbf{H}$), 4.78 (s, 1/2 H, $-C\mathbf{H}O-$), 4.68 (s, 1/2 H, $-C\mathbf{H}O-$), 3.82 (s, 3/2 H, $-OC\mathbf{H}_3$), 3.74 (s, 3/2 H, $-OC\mathbf{H}_3$), 3.25 (br d, J = 8 Hz, 1/2 H, $-C\mathbf{H}CH_2-$), 2.72 (dd, J = 8, J' = 3 Hz, 1/2 H, $-C\mathbf{H}CH_2-$), 2.65 (complex m, 1/2 H), 2.50 (d, J = 16 Hz, 1/2 H), 2.45 (complex m, 1/2 H), 0.34 (d, J = 16 Hz, 1/2 H), 2.30-2.05 (complex, 2 H), 1.90 (s, 3/2 H, -C(C$\mathbf{H}_3$)=), 1.79 (s, 3/2 H, -C(C$\mathbf{H}_3$)=), 1.25 (s, 3/2 H, -C$\mathbf{H}_3$), 1.20 (s, 3/2 H, -C$\mathbf{H}_3$), 1.12 (s, 3/2 H, -C$\mathbf{H}_3$), 1.10 (s, 3/2 H, -C$\mathbf{H}_3$), 0.88 (s, 9/2 H, -SiC(C$\mathbf{H}_3$)$_3$), 0.86 (s, 9/2 H, -SiC(C$\mathbf{H}_3$)$_3$), 0.14 (s, 3/2 H, -SiCC$\mathbf{H}_3$), 0.12 (s, 3/2 H, -SiCC$\mathbf{H}_3$), 0.08 (s, 3/2 H, -SiCC$\mathbf{H}_3$) and 0.05 (s, 3/2 H, -SiCC$\mathbf{H}_3$); ir (CHCl$_3$ cast) 1750 (ester), 1732 (ketone) and 1250 cm^{-1} (Si-CH$_3$); ms M$^+$ 366.2226 (calcd. for $C_{21}H_{34}O_4Si$: 366.2226).

(1S*, 6R*)-6-Carbomethoxy-4,9,9-trimethyl-3-t-butyldimethylsilyloxybicyclo[4.3.0]non-3-en-7-one (74).

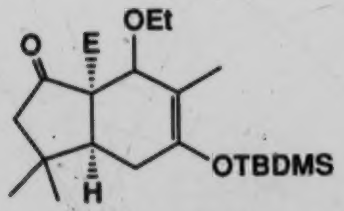


74

Adduct 74: ^{1}H nmr (400 MHz, CDCl$_3$) δ 3.70 (s, 3 H, -OC$\mathbf{H}_3$), 2.87 (d, J = 8.5 Hz, 1 H, -C$\mathbf{H}$CHHC(OTBDMS)=), 2.76 (dd, J = 16.5, J' = 1.5 Hz, 1 H, -C$\mathbf{H}$HC(CH$_3$)=), 2.41 (d, J = 18 Hz, 1 H, -C$\mathbf{H}$HCO-), 2.34 (d, J = 18 Hz, 1 H, -CH$\mathbf{H}$CO-), 2.26 (ddd, J = 18, J' = 8.5, J'' = 1.5 Hz, 1 H, -CHC$\mathbf{H}$HC(OTBDMS)=), 2.11 (d, J = 16.5 Hz, 1 H, -C$\mathbf{H}$HC(CH$_3$)=), 2.03 (d, J = 18 Hz, 1 H, -CHCH$\mathbf{H}$C(OTBDMS)=), 1.60 (s, 3 H, -CHHC(C$\mathbf{H}_3$)=), 1.20 (s, 3 H,

$-C(C\mathbf{H}_3)_2$), 0.90 (complex, 12 H, $-C(C\mathbf{H}_3)_2$, $-SiC(C\mathbf{H}_3)_3$) and 0.20 (complex, 6 H, $-Si(C\mathbf{H}_3)_2$); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 213.5 (p), 172.1 (p), 141.8 (p), 107.9 (p), 58.7 (p), 52.9 (p), 52.7 (a), 48.2 (a), 36.8 (p), 32.8 (p), 30.2 (a), 25.9 (p), 25.8 (a), 25.6 (a), 23.7 (p), 18.1 (a), 16.1 (p), -3.80 (a) and -4.00 (a); ir ($CHCl_3$ cast) 1753 (ester), 1732 (ketone) and 1190 cm^{-1} (Si-C); ms M^+ 366.2227 (calcd. for $C_{20}H_{34}O_4Si$: 366.2227). Anal. calcd. for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.36; found: C, 64.93; H, 9.70.

(1S*, 6S*)-6-Carbomethoxy-5-ethoxy-3-*tert*-butyldimethylsilyloxy-4,9,9-trimethylbicyclo[4.3.0]non-3-en-7-one (78 and 79).



E = $COOCH_3$

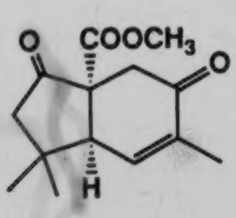
78 and79

Adduct 78: ^1H nmr (400 MHz, $CDCl_3$) δ 4.49 (br s, 1 H, $-C\mathbf{H}(OEt)$), 3.65 (s, 3 H, $-OCH_3$), 3.46 (q, J = 7 Hz, 1 H, $-OC\mathbf{H}HCH_3$), 3.35 (q, J = 7 Hz, 1 H, $-OCH\mathbf{H}CH_3$), 2.91 (dd, $J = J'$ = 8 Hz, 1 H, $-C\mathbf{H}CHHC(OTBDMS)=$), 2.46 (ddq, J = 15, J' = 8, J'' = 1.5 Hz, 1 H, $-CHC\mathbf{H}HC(OTBDMS)=$), 2.43 (d, J = 17 Hz, 1 H, $-C\mathbf{H}HCO-$), 2.25 (d, J = 17 Hz, 1 H, $-CH\mathbf{H}CO-$), 2.08 (dd, J = 15, J' = 8 Hz, 1 H, $-CHCH\mathbf{H}C(OTBDMS)=$), 1.71 (d, J = 1.5 Hz, 3 H, $-CHHC(C\mathbf{H}_3)=$), 1.05 (dd, $J = J'$ = 7 Hz, 3 H,

-OCH$_2$C**H**$_3$), 0.96 (s, 9 H, -OSiC(C**H**$_3$)$_3$), 0.90 (s, 3 H, -C(C**H**$_3$)$_2$), 0.86 (s, 3 H, -C(C**H**$_3$)$_2$), 0.12 (s, 3 H, -Si(C**H**$_3$)$_2$), and 0.11 (s, 3 H, -Si(C**H**$_3$)$_2$); ^{13}C nmr APT (100.6 MHz, CDCl$_3$) δ 211.1 (p), 171.1 (p), 149.0 (p), 112.2 (p), 80.0 (a), 67.2 (p), 65.2 (p), 54.5 (p), 52.6 (a), 49.0 (a), 35.4 (p), 31.4 (a), 28.5 (p), 26.2 (a), 25.7 (a), 23.9 (a), 18.1 (p), 15.9 (a), 15.3 (a), -3.84 (a) and -3.95 (a); ir (CHCl$_3$ cast) 1753 (ester), 1728 (ketone), 1679 (enol) and 1253 cm^{-1} (Si-C); ms M$^+$ (CI) 411 (calcd. for $C_{20}H_{34}O_4Si$: 410.2488). Anal. calcd. for $C_{20}H_{34}O_4Si$: C, 64.35; H, 9.33; found: C, 64.10; H, 9.50.

Adduct 79: ^{1}H nmr (400 MHz, CDCl$_3$) δ 4.35 (s, 1 H, -C**H**(OEt)), 3.68 (s, 3 H, -OC**H**$_3$), 3.42 (q, *J* = 7 Hz, 2 H, -OC**H**$_2$CH$_3$), 3.16 (dd, *J* = 7.5, *J'* = 1.5 Hz, 1 H, -C**H**CHHC(OTBDMS)=), 2.71 (ddq, *J* = 16.5, *J'* = 7.5, *J''* = 2 Hz, 1 H, -CHC**H**HC(OTBDMS)=), 2.16 (d, *J* = 17 Hz, 1 H, -C**H**HCO-), 2.07 (d, *J* = 17 Hz, 1 H, -CH**H**CO-), 2.05 (dd, *J* = 16.5, *J'* = 1.5 Hz, 1 H, -CHCH**H**C(OTBDMS)=), 1.63 (d, *J* = 2 Hz, 3 H, -CH(OEt)C(C**H**$_3$)=), 1.09 (t, *J* = 7 Hz, 3 H, -OCH$_2$C**H**$_3$), 0.98 (s, 3 H, -C**H**$_3$), 0.95 (s, 12 H, -OSiC(C**H**$_3$)$_3$, -C**H**$_3$), 0.14 (s, 3 H, -Si(C**H**$_3$)$_2$) and 0.13 (s, 3 H, -Si(C**H**$_3$)$_2$); ^{13}C nmr APT (100.6 MHz, CDCl$_3$) δ 210.2 (p), 169.4 (p), 149.9 (p), 110.7 (p), 81.5 (a), 67.7 (p), 64.4 (p), 53.0 (p), 52.6 (a), 46.0 (a), 36.7 (p), 30.5 (a), 29.0 (p), 25.6 (a), 24.7 (a), 18.0 (p), 16.2 (a), 15.3 (a), -3.7 (a) and -4.1 (a); ir (CHCl$_3$ cast) 1755 (ester), 1732 (ketone), 1679 (enol) and 1229 cm^{-1} (Si-C).

(1R*, 6S*)-1-Carbomethoxy-4,7,7-trimethylbicyclo[4.3.0]non-4-en-3,9-dione (65).

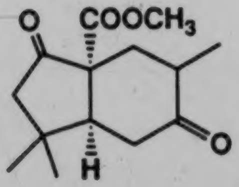


65

Oxygen was passed for 10 min through a dichloromethane (0.5 mL) solution of keto ester **63** (25 mg, 0.10 mmol), dry pyridine (15 μL, 0.18 mmol), acetic anhydride (20 μL, 0.21 mmol), a catalytic quantity of 4-dimethylaminopyridine (~5 mg) and a catalytic quantity of 5,10,15,20-tetraphenyl-21 *H*, 23 *H*-porphine (~5 mg). The solution was irradiated with a tungsten lamp (200 W) for 10 h while oxygen was continuously passed through the solution. The reaction was quenched with a saturated aqueous sodium bicarbonate solution (1 mL) and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The organic extracts were combined and washed with 10 % aqueous HCl (3 x 2 mL), saturated aqueous copper(II) sulfate (1 x 2 mL) and brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (0-10 % ether in petroleum ether) gave recovered keto ester **63** (5 mg, 20 %). Further elution gave diketone **65** as a colorless oil (9 mg, 0.036 mmol, 41 % yield): ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.58 (dq, *J* = 5, *J'* = 2 Hz, 1 H, -CHC**H**=C(CH_3)CO-), 3.72 (s, 3 H,

-OCH_3), 3.31 (dq, *J* = 5, *J'* = 1.5 Hz, 1 H, -C**H**CH=C(CH_3)CO-), 3.14 (d, *J* = 17 Hz, 1 H, -C**H**HCOC(CH_3)=), 2.69 (d, *J* = 17 Hz, 1 H, -CH**H**COC(CH_3)=), 2.46 (d, *J* = 11 Hz, 1 H, -C**H**HCO-), 2.42 (d, *J* = 11 Hz, 1 H, -CH**H**CO-), 1.85 (dd, *J* = 2, *J'* = 1.5 Hz, 3 H, -CHCH=C(C**H**$_3$)CO-), 1.40 (s, 3 H, -C**H**$_3$) and 1.05 (s, 3 H, -C**H**$_3$); ir ($CHCl_3$ cast) 1753 (ester), 1732 (ketone) and 1679 cm^{-1} (enone); ^{13}C nmr APT (100.6 MHz, $CDCl_3$) δ 211.0 (p), 194.4 (p), 171.8 (p), 139.1 (a), 136.3 (p), 63.7 (p), 55.1 (p), 53.3 (a), 51.4 (a), 38.5 (p), 38.4 (p), 28.6 (a), 25.2 (a) and 16.3 (a); ms M^+ 250.1204 (calcd. for $C_{14}H_{18}O_4$: 250.1205).

(1S*, 6R*)-6-Carbomethoxy-4,9,9-trimethylbicyclo[4.3.0]nonan-3,7-dione (75).

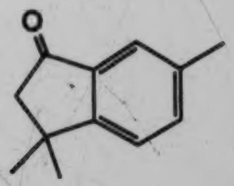


75

Silyl enol ether **74** (50 mg, 0.14 mmol) was hydrolyzed in tetrahydrofuran (2 mL) with aqueous 0.1 N hydrochloric acid solution (1 mL). The solution was stirred at room temperature for 24 h. Water (2 mL) was added to the reaction container and the aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were washed with water (2 x 2 mL) and brine (1 x 1 mL), dried ($MgSO_4$), filtered and concentrated.

Purification of the resulting oil by flash chromatography over silica gel (0-5 % ether in petroleum ether) gave the epimeric mixture **75** (3.8 : 1) as a colorless oil (29 mg, 0.11 mmol, 78 %) : ^{1}H nmr (400 MHz, $CDCl_3$): major isomer: δ 3.77 (s, 3 H, -OC**H**$_3$), 3.16 (ddd, J = 7.5, J' = 5, J'' = 1 Hz, 1 H), 2.75-2.30 (complex, 4 H), 1.61 (dd, J = J' = 9 Hz, 1 H), 1.35 (dd, J = 6, J' = 1 Hz, 2 H), 1.18 (br s, 3 H, -C**H**$_3$), 1.02 (s, 3 H, -C**H**$_3$) and 0.95 (s, 3 H, -C**H**$_3$); minor isomer: 3.72 (s, 3 H, -OC**H**$_3$), 3.09 (dd, J = 7.5, J' = 5.5 Hz, 1 H), 1.96 (dd,J = 12, J' = 9 Hz, 1 H), 1.15 (br s, 3 H, -C**H**$_3$), 1.06 (s, 3 H, -C**H**$_3$) and 0.91 (s, 3 H, -C**H**$_3$), other peaks were overlapped with those of the major isomer; ^{13}C nmr APT (100.6 MHz, $CDCl_3$): major isomer: δ 211.9 (p), 211.5 (p), 171.5 (p), 59.1 (p), 53.3 (p), 53.1 (a), 50.7 (a), 40.6 (a), 37.2 (p), 37.0 (p), 34.8 (p), 29.3 (a), 24.5 (a) and 14.4 (a); minor isomer: δ 212.8 (p), 211.2 (p), 172.2 (p), 63.7 (p), 59.9 (p), 51.9 (p), 48.9 (a), 40.2 (a), 38.5 (p), 36.2 (p), 30.2 (a), 24.9 (a), 17.7 (a) and 15.3 (a); ir ($CHCl_3$ cast) 1751 (ester), 1716 cm^{-1} (broad, ketones); ms M$^+$ 252.1359 (calcd. for $C_{14}H_{20}O_4$: 252.1356).

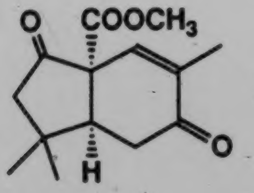
3,3,6-Trimethyl-2,3-dihydro-1*H*-inden-1-one (76)



76

Compound **70A/71A** (24 mg, 0.074 mmol) was dissolved in 2,4,6-collidine (1 mL) under an argon atmosphere. Anhydrous lithium iodide (50 mg, 0.37 mmol) was added followed by water (14 μL, 0.74 mmol). The mixture was refluxed for 4 h, cooled down and poured into aqueous 5 % hydrochloric acid (2 mL) and the aqueous layer was extracted with ether (3 x 2 mL). The organic layer was washed with aqueous 5 % hydrochloric acid (2 x 2 mL), water (1 x 2 mL) and brine (1 x 2 mL), dried ((MgSO$_4$), filtered and concentrated. Purification by flash chromatography on silica gel (0-3 % ether in petroleum ether) gave pure compound **76** (7 mg, 54 %): ^{1}H nmr (400 MHz, CDCl$_3$) δ 7.50 (br s, 1 H, C-7 H), 7.44 (dd, J = 8, J' = 1 Hz, 1 H, C-5 H), 7.38 (d, J = 8 Hz, C-4 Hz), 2.60 (s, 2 H, -C**H**$_2$CO-), 2.40 (s, 3 H, C-6 -C**H**$_3$) and 1.40 (s, 6 H, -C(C**H**$_3$)$_2$); ir (CHCl$_3$ cast) 1736 cm^{-1} (ketone) and 825 cm^{-1} (aromatic); ms M$^+$ 174.1043 (calcd. for C$_{12}$H$_{14}$O: 174.1042).

(1S*, 6R*)-6-Carbomethoxy-4,9,9-trimethylbicyclo[4.3.0]non-4-en-3,7-dione (80).



80

Silyl enol ether **80** (115 mg, 0.28 mmol) was hydrolyzed in tetrahydrofuran (2 mL) with aqueous 0.1 N hydrochloric acid solution (1 mL). The solution was stirred at room temperature for 24 h before water (2 mL) was added to the reaction. The aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were washed with water (2 x 2 mL) and brine (1 x 1 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resulting oil by flash chromatography on silica gel (0-10 % ether in petroleum ether) gave compound **80** as a colorless oil (50 mg, 0.20 mmol, 70 %): ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.69 (dq, *J* = *J'* = 1 Hz, 1 H, -C**H**=C(CH_3)CO-), 3.77 (s, 3 H, -OC**H**$_3$), 3.17 (ddd, *J* = *J'* = 5, *J''* = 1 Hz, 1 H, -C**H**CH_2CO-), 2.67 (d, *J* = 5 Hz, 2 H, -CHC**H**$_2$CO-), 2.50 (d, *J* = 17 Hz, 1 H, -C**H**HCO-), 2.29 (d, *J* = 17 Hz, 1 H, -CH**H**CO-), 1.83 (d, *J* = 1 Hz, 3 H, -CH=C(C**H**$_3$)CO-), 1.24 (s, 3 H, -C**H**$_3$) and 0.79 (s, 3 H, -C**H**$_3$); ^{13}C nmr DEPT (100.6 MHz, $CDCl_3$) δ 209.0 (s), 196.3 (s), 169.5 (s), 138.8 (d), 136.9 (s), 60.7 (s), 53.7 (t), 53.4(q), 48.2 (d), 37.6 (t), 33.9 (t), 27.6 (q), 23.5 (q) and 16.0 (q); ir ($CHCl_3$ cast) 1756 (ester), 1727 (ketone) and 1679 cm^{-1} (enone); ms M^+ 250.1200 (calcd. for $C_{14}H_{18}O_4$: 250.1205). Anal. calcd. for $C_{14}H_{18}O_4$: C, 67.17; H, 7.25; found: C, 67.04; H, 7.16.

References

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